SUSTAINED DELIVERY OF SERTACONAZOLE THROUGH MICROSPONGE BASED GEL FORMULATIONS

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Submitted by

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OCTOBER– 2017

CERTIFICATE OF APPROVAL

The foregoing thesis entitled **SUSTAINED DELIVERY OF SERTACONAZOLE THROUGH MICROSPONGE BASED GEL FORMULATIONS** is hereby approved as creditable study of research topic and has been presented in satisfactory manner to warrant its acceptance as prerequisite to the degree for which it has been submitted.

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DECLARATION

We hereby declare that the matter embodied in the dissertation entitled **"SUSTAINED DELIVERY OF SERTACONAZOLE THROUGH MICROSPONGE BASED GEL FORMULATIONS"** is a bonafide and genuine research work carried by me under the guidance of **Mr. D. SAKTHIVEL** M.Pharm., (Ph.D)**.,** Associate Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, NH-7, Karur Main Road, Namakkal-637207.

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By

PRIYADHARSHINI.M

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ABSTRACT

Sertaconazole is an imidazole derivative, which acts as fungistatics, fungicidal, antibacterial, anti inflammatory, antitrichomonal, antipruritic. Present study was taken up to develop a topical formulation that releases the drug in controlled manner, reduce the side effects associated with topical drug delivery and improve product efficiency with aid of microsponges. Microsponges loaded with Sertaconazole were prepared by using quasi emulsion solvent diffusion with seven different proportions of polymer Eudragit RS100. The developed microsponges were analysed for particle size, production yield, entrapment efficiency and drug content. Scanning electron microscopic images of microsponges revealed that they are spherical in shape and contain pores. In vitro drug release results depicted that microsponges with 1:7 drug polymer ratio were more efficient to give extended drug release of 92.02% at the end of 24 hrs. Microsponge were then incorporated in to 1% carbopol gel and evaluated for pH, viscosity spredability and diffusion study. Thus the formulated microsponges based gel of Sertaconazole would be a promising alternative to conventional therapy for safer and efficient treatment of various skin disorders like Athelete's foot and Tineapedis.

Keywords: Microsponges, Sertaconazole, Eudragit RS100, Controlled drug release, Drug content.

Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect in human or animals[2]. For decades the acute and chronic illness are clinically treated through delivery of drug to patients in form of *pharmaceutical dosage forms*, like tablet, capsule, pills, creams, liquids, ointments, aerosols, injectables and suppositories, which are referred to as *conventional dosage form.* The Conventional dosage forms have many disadvantages.

For maintaining effective concentration of drugs in plasma, it is often necessary to administer the drug several times. Failure in maintaining the effective concentration can cause fluctuation in drug levels in plasma and lead to poor patient compliance. The conventional dosage forms delivering the minimal effective concentration of drug at required site or organs, sometimes tend to get into general circulation, at higher concentration leading to unwanted side effects. Inorder to overcome the drawbacks of the conventional dosage form and to improve the safety and efficacy of drugs, several attempts have been made for delivering these active moiety in existing desired concentration lead to the development of drug delivery system. The drug delivery system are the engineered technologies for the targeting/controlling the release of therapeutic agents to the desired site.

Drug delivery system control the rate at which the drugs are released in to the desired part of body. The devices used in new drug delivery approach come under two main headings “sustained release system and “controlled release system”. Sustained release system: These are delivery systems formulated to retard the release of therapeutic agent such that, its release of drug into the systemic circulation are delayed and or prolonged. The onsets of its pharmacologic action are often delayed, and the duration of its therapeutic effect is sustained.

Controlled release system: The release of therapeutic moiety from controlled drug delivery system, proceeds at a control and the rate can be predicted kinetically and also reproducible from one unit to another[1].The majority of controlled release dosage forms are designed for oral administration. Recently the controlled delivery systems are also introduced in,

- Oral Drug Delivery System
- Mucosal Drug Delivery System

- Nasal Drug Delivery System
- Parenteral Drug Delivery System
- Vaginal Drug Delivery System
- Intrauterine Drug Delivery System
- Ocular Drug Delivery System
- Transdermal Drug Delivery System

Advantages of controlled release preparation[3]

- Decreases the incidence and/or intensity of adverse effects and toxicity.
- Better drug utilization.
- More uniform drug concentration in blood.
- Improved patient compliance.
- Reduced the dosing frequency.
- More consistent and prolonged therapeutic effect.

Topical delivery

Topical delivery includes two basic types of product

- External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.
- Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity[4].

For the most part topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying of skin or mucous membranes. Although some united drug absorption may occur, it is sub therapeutics quantities and generally of minor concern[3].

Advantages of topical drug delivery system.[4, 7]

- Avoidance of first pass metabolism
- Convenient and easy to apply.

- Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time.
- Achievement of efficacy with lower total daily dosage of drug by continues drug input.
- Avoids fluctuation in drug levels, inter- and intrapatient variations.
- Ability to easy terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Ability to deliver drug more selectively to specific site.
- Avoidance of gastro intestinal incompatibility.
- Providing utilization of drug with short biological half life, narrow therapeutic window.
- Improving physiological and pharmacological response.
- Improve patient compliance
- Provide suitability for self medication.

Disadvantages of topical drug delivery systems[8, 10]

- Skin irritation of contact dermatitis may occur to the drug or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergic reaction.
- Can be used only for drugs which require very small plasma concentration for action.
- Enzyme in epidermis may denature the drug.
- Drugs of large particle size not easy to absorb through the skin

Classification of topical drug delivery systems[11]

Classification based on physical state

(a) Solid

- Powder
- Aerosol
- Plaster

(b) Liquid

- Lotion
- Liniment
- Solution
- Emulsion
- Suspension
- Aerosol

(c) Semi solid

- Ointment
- Cream
- Paste
- Gel
- Jelly

Skin characteristics[12, 13]

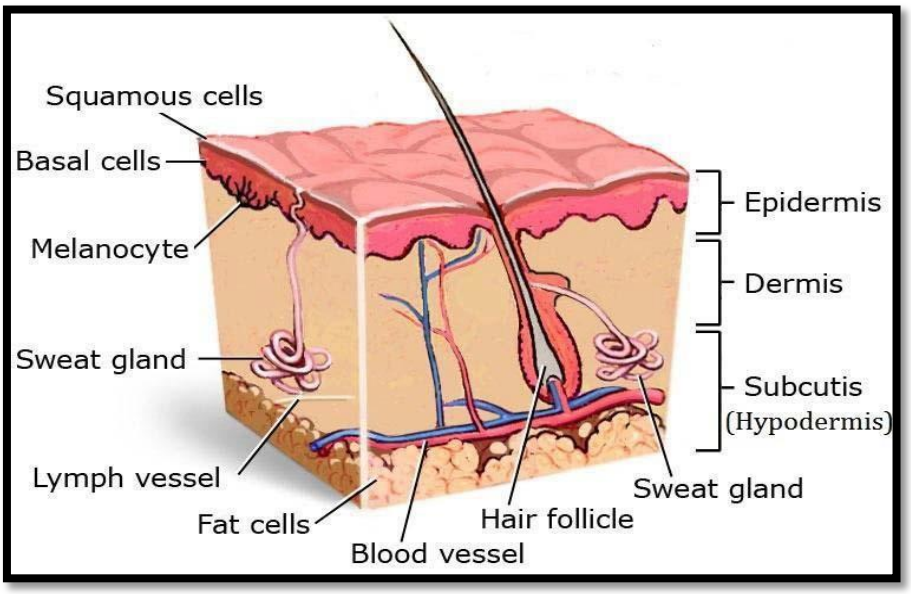
The skin is not only a protective rap for the body, but also busy frontier which mediates between the organism and the environment. It not only controls the loss of valuable fluid , but also prevents the penetration of noxious foreign materials and radiation and cushions against mechanical stock, but also regulates heat loss and transduces incoming stimuli.

The skin is an organ because it consists of tissues, structurally joined together to perform specific activities and has a large surface area. Basal surface area of an average adult skin is approximately 2,500cm^2 and it weight about 4.8kg in men and 3.2kg in women.

The purpose of topical dosage form is to conveniently deliver drugs to localized area of the skin. It is necessary to understand the characteristics of skin to develop an ideal topical dosage forms.

Anatomy of skin

Figure: 1



THE SKIN: The site of precutaneous absorption

Anatomy and physiology of skin: Human skin comprises of three distinct but mutually dependent tissues[14, 17]

a. The stratified, vascular, cellular epidermis,
b. Underlying dermis of connective tissues and
c. Hypodermis.

The Epidermis

The multilayered epidermis varies in thickness,depending on cell size and number of cell layers of epidermis, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Epidermis consists outer stratum corneum and viable epidermis.

Stratum corneum

This is the outermost layer of skin also called as horney. It is approximately 10mm thick when dry but swells to several times this thickness when fully hydrated. Stratum corneum contains 10 to 25 layers of dead, keratinized cells called corneocytes.

The layer are flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration of drug. The architecture of horney layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein “bricks” embedded in lipid “mortar.” The lipids are arranged in multiple bilayers. There is sufficient amphiphilic material in the lipid fraction, such as polar free fatty acids and cholesterol, to maintain a bilayer form.

Viable epidermis

The viable epidermis is situated beneath the stratum corneum and varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms. As one go deeper, consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basal. In the basal layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horney cells from the skin surface. As the cells produced by the basal layer move outward, they get altered morphologically and histochemically, undergoing keratinization to form the outermost layer of stratum corneum.

Dermis

Dermis is 3 to 5mm thick layer and is composed of a matrix of connective tissue, which contains blood vessels, lymph vessels and nerves. The cutaneous blood supply has essential function in regulation of body temperature. The layer also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of a permeant very low and the resulting concentration difference across the epidermis provides the essential concentration gradient for transdermal permeation.

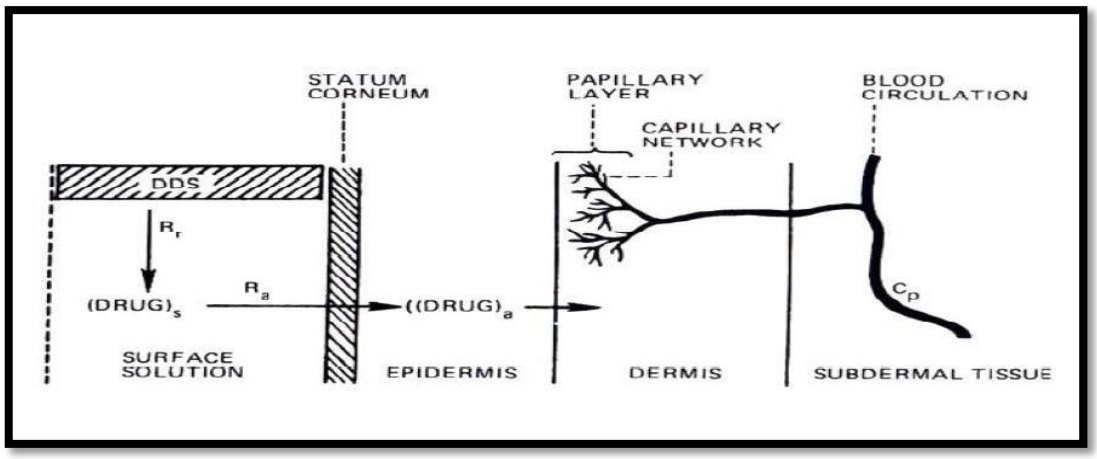
Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to

penetrate through all these three layers and reach into systemic circulation while in case of topical drug delivery only penetration through stratum corneum is essential and then retention of drug in skin layers is desired.

MECHANISM OF PRECUTANOUS ABSORPTION

Figure: 2 Mechanism of precutanous absorption

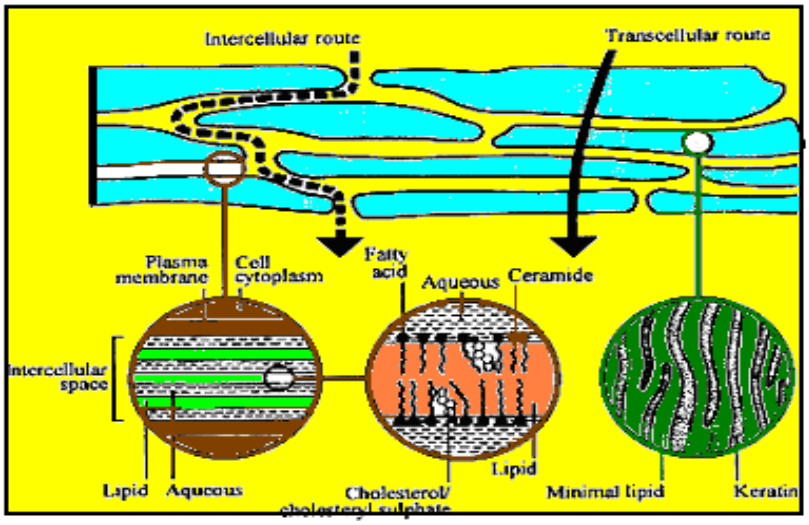


There are three pathways (Figure 2) which can be involved in the transdermal permeation of

chemicals:

1. Through the intercellular lipid domains in SC
2. Through the skin appendages; and
3. Through the keratin bundles in SC.

Figure: 3 Pathway of transdermal permeation



There are three possible ways that drug molecules can pass through stratum corneum.

1. Transfollicular route
2. Transcellular route
3. Intercellular route

The drug can be absorbed by various pathways through the skin depending on the physicochemical properties of the drug. Both lipophilic and hydrophilic drugs are absorbed from different routes.[18, 19]

Transfollicular route; Transfollicular route is the shortest pathway that drug has to pass and reach the systemic circulation. This route provides a large area for drug diffusion. Skin has various sweat glands, oil glands, hair follicles and pores opening to the outer surface of the skin via their ducts. These ducts offer a continuous channel across the stratum corneum for drug transport. The factors that affect the drug transport are secretion from glands, content and amount of secretion etc. However this route occupies only 0.1% of total skin surface and therefore contributes a little.[20, 21]

Transcellular route; The transcellular route is suitable for hydrophilic drugs. The drug passes through the corneocytes of stratum corneum. The highly hydrated keratin provide aqueous pathway to the hydrophilic drugs. A number of partitioning and diffusion steps are needed to pass the drug through the cell matrix.[21, 22]

Intercellular route: As the name indicates the intercellular route the drug diffuses through the lipid bilayer between the cells. In this route, the molecule stays in the lipid bilayer and winds around the keratinocytes on its way to the dermis. Although both paths are possible, the most common route of drug penetration is the intercellular route because most drug molecules are more soluble in the lipid environment of the bilayer than in the protein environment of the keratinocytes.[22, 23]

Microsponge: An approach for topical delivery

Over the past 40 years, the ability to control the delivery rate of active agents to a predetermined site in the human body has been one of the biggest challenges till date met by continued innovative solutions by the medical profession and drug industry. Because of this some areas of pharmaceutical research have been focused on the controlled delivery of systemic drugs.[24]

Various predictable and reliable systems have been developed for systemic drugs under the title of trasdermal delivery systems using the skin as portal entry. Transdermal patches developed in 1970's improved the delivery of drugs such as nitro glycerine and scopolamine resulting in better control of therapeutic dose, simpler dosage regimens, and fewer side effects than the more traditional oral or parentral administration of the same drug. And more over these devices mimicked the intravenous administration of the drug which is not patient compliance.[25] In general, these delivery systems have improved the efficiency and safety of various drugs. Controlled release of drugs on to the epidermis assure that the drug remains primarily localized and does not enter the systemic circulation in significant amount thereby minimizing the side effects.

Although transdermal delivery systems can be efficient in supplying drugs for systemic effects they are not practical for controlling the delivery of materials whose final target is the skin itself.[26]

No efficient vehicle have been developed for the controlled and localized delivery of drugs in to the stratum corneum and underlying skin layers.

Yet there are many instance when epidermal localization of a drug is desirable, but absorption beyond the epidermis undesirable.[27]

Corticosteroids are the suitable examples for these problems. Although corticosteroids are effective for skin disorders, their topical application results in significant systemic absorption; this may leads to unwanted side effects such as adrenal suppression or interference with immune functions.

The same is true in case of cosmetics like sunscreens, winter cares and drugs for the treatment of epidermal infection and allergies like acne, eczema, hyper pigmentation etc. it is necessary to maximize/lengthen the time of residence of these active ingredient

on the skin surfaces or within the outer layers of the epidermis while minimizing its trasepidermal penetration into the body[28].

Another problem with the application of topical drug is the most of the vehicles, such as ointment, often prove aesthetically unappealing; greasiness stickiness or even discoloration in clothing can make daily ware unpleasant.[29]

This frequently results in patient incompliance, many of these conventional vehicles require high concentration of active ingredients for effective therapy because of their low efficiency as a delivery system. As a result, irritation or allergic response can be elicited in a significant percentage of users.

Other disadvantages of conventional topical delivery system are the uncontrolled evaporation of active ingredient, unpleasant odour, and the potential incompatibility of one or more drugs with each other or with the vehicle.[30]

Moreover conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically such products release their active ingredients upon application, producing a highly concentrated layer of active ingredients that is rapidly absorbed. This causes systemic side effects.[29]

Thus, there is a need to develop a delivery system to maximize residence time of the active pharmaceutical ingredient (API) in the skin. Such a new system would possibly increase the efficacy of the topically active agents while enhancing product safety. The microsponges are polymeric delivery devices which contain active ingredients with release API onto the skin over of time in response to a trigger.

MICROSPONGE TECHNOLOGY[27]

Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents[30]. Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, This company developed a large number of

variations of the technique and applied those to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products.

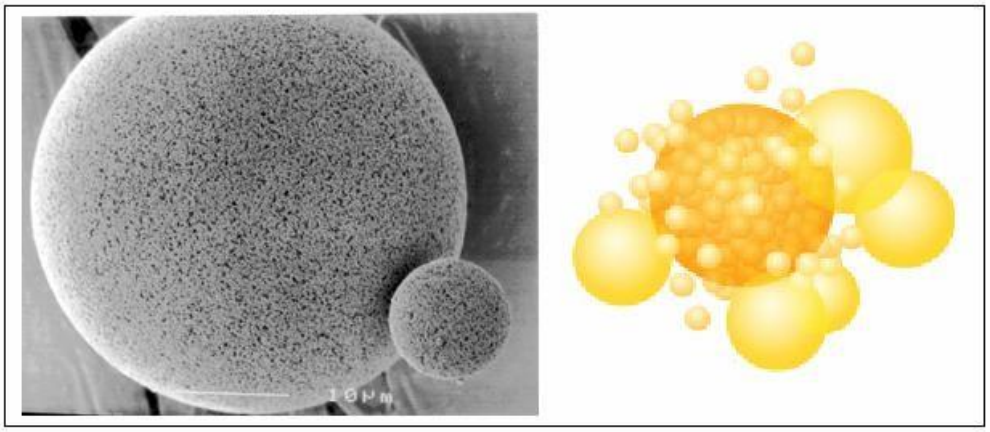
Structure of microsponges

The size of the microsponges can be varied, usually from 5 – 300 μm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 μm[31] sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 μm cannot penetrate into the tunnel structure of the microsponges.

Reslease of active ingredients from conventional topical formulation over an extended period of time is quite difficult. These vehicles high concentration of active agents for effective therapy because of their low efficacy of delivery system, resulting in to irritation and allergic reaction in significant users. In contrast, microsponge technology allow an even and sustained rate of release, reducing irritation while maintaining efficacy. Their high degree of cross linking result in particles that are insoluble, inert of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, lotion, and powder.[31]

Their characteristic feature is the capacity to adsorb or ” load” a high degree of active materials into the particles and on its surface. Its large capacity for entrapment of actives, up to three times its weight, differentiate microsponge products from other types of dermatological delivered system.

Figure: 4 View of Microsponges



Characteristics of microsponges [32, 33]

- MDS have stable over ranges of pH 1 to 11
- They are stable at temperature 130° C
- They are compatible with most vehicles and ingredients
- Free flowing and cost effective
- They have higher pay load is up to 50 – 60%
- Microsponge formulations are self sterilizing as their average pore size is 0.25um where bacreia cannot penetrate.

Advantages of MDS [34, 35]

- Microsponges are microscopic sphere capable of absorbing skin secretions, therefor reducing oiliness and shine from the skin(absorb oil up to 6 times its weight without drying)

  Eg :- oil free matte block spf20
- It provide continuous action up to 12 hrs i.e. extended release[36,37,38]

  Eg :- Epi Quin Micro

  The microsponge system uses microscopic reservoirs that entrap Hydroquinone and retinol.

  The MDS release these ingredients into the skin gradually throughout the day.Improve thermal, chemical, and physical stability.

- These are non-irritating, non mutagenic, non allergic and non toxic.
  Eg :- carac cream, 0.5%

Advantages over conventional formulation

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed.[39] When compare to the Microsponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially, the Microsponge system can reduce significantly the irritation of effective drugs without reducing their efficacy. For example, by delivering the active ingredient gradually to the skin like MDS-Benzoyl peroxide formulation have excellent efficacy with minimal irritation[40.]

Advantages over microencapsulation and liposomes[41]

The MDS has advantages over other technologies like microencapsulation and liposome. Microcapsule cannot usually control the release rate of actives. Once the wall is ruptured the active contained within microcapsules will be released. Liposome does suffer from lower paylod, difficult formulation, limited chemical stability and microbial instability. While microsponge system in contrast to the above system are stable over range of pH 1 to 11, temperature up to 130^0 C compatible with most vehicle and ingredients, self sterilizing as average pore size is 0.25um where bacteria cannot penetrate higher paylod (50-60%) still free flowing and can be cost effective.[42]

Advantages over ointments

Ointments are often aesthetically unappealing, greasiness, stickiness etc. that often results into lack of patient compliance[43]. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odour and potential incompatibility of drugs with the vehicles, when microsponge system

maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body [44] .

Characteristic of actives that is entrapped into microsponges

- It shoulbe either miscible in monomer[45] as well as capable of being made miscible by addition of small amount of a water immicible solvent.
- It should be inert to monomers and should not increase the viscosity of the mixture during formulation.
- It should be water immiscible or nearly only slightly soluble.
- It should not collapse spherical structure of the microsponge.
- It should be stable in contact with polymerization[46] catalyst and also in conditions of polymerization.
- Not more than 10 to 12%wlw microsponges must be incorporated in to the vehicle in order to avoid cosmetic problems.
- Paylod and polymer design of the microsponges for active must be optimized for required release rate for given period of time.

Polymers used in Microsponge preparation

There are various polymer, which are used in preparation of microsponges. Usually monomers like styrene, Di vinyl benzene, Ethyl vinyl benzene and methyl methacrylate are employed in liquid -liquid suspension polymerization technique. Where Eudragit RS100 and carbopol were employed for quasi emulsification technique. None of the above mentioned polymer were found to be superior to others when properties were compared. Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups. Eudragit polymer are available in a wide range of different physical forms. Eudragit RS100 is employed for quasi emulsification technique.

Method of preparation of microsponges[47,48,49]

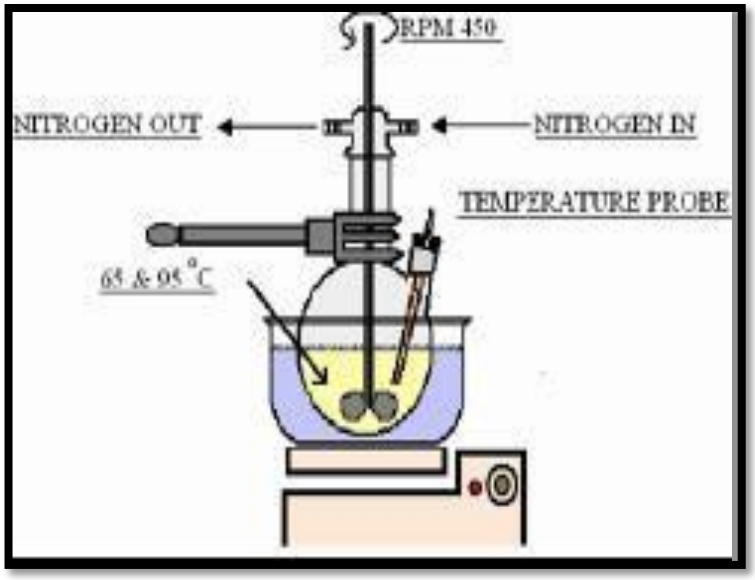
Based on the physio chemical properties of the drug to be incorporated in microsponge, this is divided in to two ways,

1. One step process or liquid liquid suspension polymerization
2. Two step process or quasi- emulsion diffusion

Liquid liquid suspension polymerization

In this method the monomers are firstly dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase with agitation. Aqueous phase typically consists of addictives such as surfactants and dispersants (suspending agent) etc inorder to facilitate the formation of suspension. Once the suspension is established with distinct droplets of the preferred size then polymerization is initiated by the addition of catalyst or by increasing temperature as well as irradiation.[50] The polymerization method leads to the development of a reservoir type of system that opens at the surface through pores. During the polymerization, an inert liquid immiscible with water however completely miscible with monomer is used to form the pore network in some case. Once the polymerization process is complete the liquid is removed leaving the microsponges which is permeate within preformed microsponges then, incorporated the variety of active substances like antifungal, anti acne, anti inflammatory etc and act as a topical carriers.[14]

Figure: 5 Liquid liquid suspension polymerization



The various steps[53] involved in the preparation of microsponges are summarized as follows

Step1: Selection of monomers and combination of monomers

Step2: Formation of chain monomers as polymerization starts

Step3: Formation of ladders as a result of cross-linking between chain monomers.

Step4: Folding of monomer ladder to form spherical particles.

Step5: Agglomeration of microsphere leads to the production of bunches of microspheres

Step6. Binding of bunches to produce microsponges.

Quasi –emulsion solvent diffusion[54]

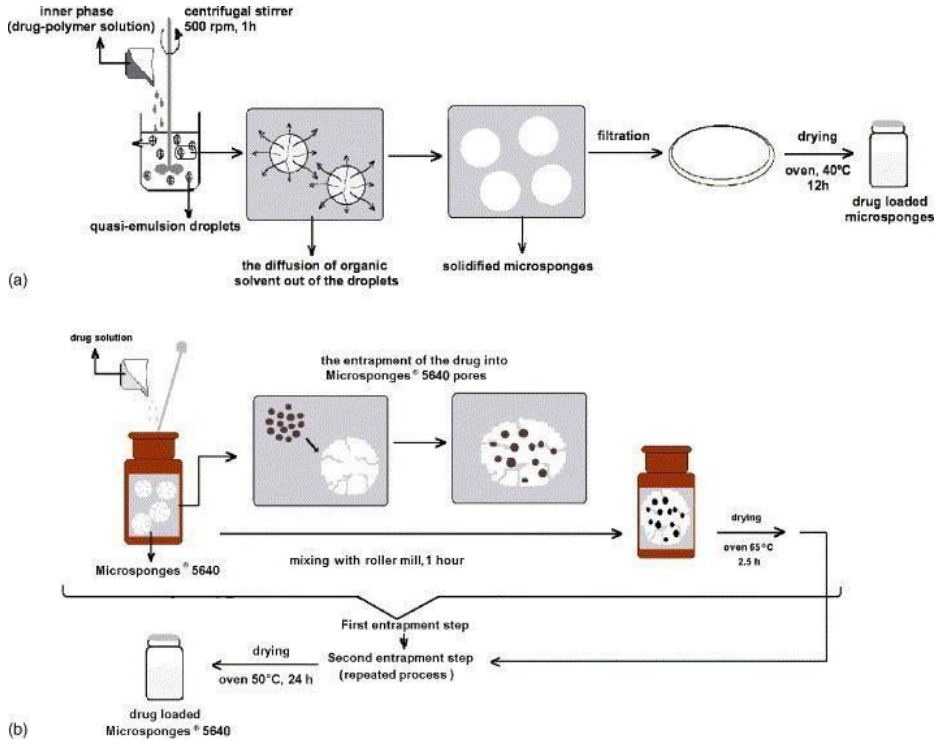
Microsponges were prepared by quasi emulsion solvent diffusion technique. In this method external phase and internal phase were used. The internal phase is organic phase containing drug, ethyl alcohol/ acetone (good solvent), polymer and Triethylcithrate(TEC)/ trichloro-methane /Dichloromethane (bridging liquid), which was added at an amount of 20% of the polymer in order to facilitate the plasticity. The external phase mostly consists of distilled water and polyvinyl alcohol (PVA).

Weighed amount of drug and polymer were dissolved in measured quantity of ethanol. The formed ethanolic solution was poured into water containing polyvinyl alcohol. The system was thermally controlled at 20°C Ethanol solution was finely dispersed in the aqueous phase as discrete droplet of the polymer solution of the drug were solidified in the aqueous phase via counter diffusion of ethanol and water out the droplets. The formed micro particle were filtered and washed with distilled water before being tray dried at room temperature.

Steps

This is a two step process where the microsponges can be prepared by quasi-emulsion solvent diffusion method using the different polymer amount

Figure: 6 Quasi –emulsion solvent diffusion



- To prepare the inner phase, Eudargit RS 100 is dissolved in ethyl alcohol.
- Then drug can be added to solution and dissolved under ultrasonication at 35°C
- The inner phase is then poured into PVA solution in water (outer phase)
- Following 60 min of stirring, the mixture is filtered to separate the microsponges.
- The microsponges are in air-heated oven at 40^0C for 12 hr and weighed to determine production yield (PY)

Drug release mechanism[55]

Microsponges can be intenteded to release given amount of active ingredients over time in response to one or more following external triggers i.e. pressure, pH, temperature change and solubility etc which are described as follows .

Temperature changed[56] :- entrapped materials, such as sunscreens and emollient can be too viscous at room temperature to flow spontaneously from the microsponge onto the skin, when warmed by the skin temperature, the sun and the other heat source , their viscosity may decrease, resulting in an increase flow rate.

pH [57] **:** The pH responsive MDS involves coating of conventional microsponge delivery system with enteric coating type of material, which imparts pH responsiveness to this system.

Pressure[58]:- rubbing or pressure applied can release the active ingredients from microsponges on to skin.

Solubility[59] :- microsponges loaded with water miscible ingredients like antiseptics and anti-perspirants will release the ingredient in the presence of water. The release can also be activated by diffusion but taking into consideration, the partition coefficient of the ingredient between the microsponges and the external system.

Effect of formulation variables on physical properties of microsponges

a) **Effect of composition of internal and external phase**

It is formed that particle size of microsponges were directly propotional to the apparent viscosity of dispersed phase. Larger the difference between apparent viscosity of dispersed and contineous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can hardly be divided in to smaller particles and bigger droplets are found resulting in a increase in mean particle size.

Good microsponges can be produce only when 3 to 5ml of internal phase is used .when the amount of internal phase is increased from 5 to 15ml , the production yield and drug content of microsponge is found to be decreased this is due to the lower concentration of the drug in the higher volume of internal phase.

b) **Effect of drug to polymer ratio**

When the amount of polymer is kept constant but the ratio of drug to polymer is varied , the drug containing capacity is not much effected by drug to polymer

ratio but the production yield can be enormously changed from minimum ratio to maximum one. Another parameters which is effected from the drug polymer ratio change is particle size. It has been observed that the drug amount is increased particle size of the microsponges is also increased.

Effect of process variables on physical properties of microsponges.

- **Effect of stirring rate**

  As the stirring rate is increased microsponge of smaller size are obtained. Increase the stirring rate decrease the production yield but the drug content get increased s the stirring rate is increased. This is due to the turbulence created within the external phase due to which polymer gets adhered to the paddle and production yield gets decreased.

Benefits[60]

The microsponge delivery system offers the following benefits:

- Liquid can be converted to powders.
- Allows for novel product forms advanced oil control – absorbs up to 6 times its weight without drying.
- Extended release – continuous up to 12 hours.
- Reduced irritation – better tolerance means broader consumer acceptance.
- Improved product aesthetics – gives product an elegant feel.

Flexibility Benefits

- Improve stability – thermal, physical, chemical.
- Allows incorporation of the immiscible.
- Improves material processing.

Application of microsponge system[61]

Microsponges are porous polymeric microspheres that are used mostly for topical and recently for oral administration. It offers the formulator arrange of alternative to develop drug and cosmetic products. Microsponges are design to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

Table: 1

Active agents	Application
Anti inflammatory. Eg ;- hydrocortisone	Long lasting activity with lessening of skin allergic response and dermatoses
Sunscreen	Long lasting product efficacy with improved protection against sunburns and sun related injuries even ateleved concentration and with reduced irritancy and sensitization.
Anti acne, eg ;- benzoyl peroxide	Maintained efficacy with decreased skin irritation and sensitization
Anti fungal	Sustained release of activities
Anti dandruff. Eg ;- selenium sulphide, zinc pyrithion	Reduced unpleasant odour with extended safty and efficacy.
Anti pruritis	Extended and improved activity
Skin depigmenting agent eg ;- hydroquinone	Improved stabilization against oxidation with improved efficacy and aesthetic appeal.
Rubefacients	Prolonged activity with reduced irritancy greasiness and odour

Marketed formulation[62, 63]

Table 2

Product	Advantage	Manufacture
Retin –A- Micro	0.1% and 0.04% tretinoin entrapped in MDS for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/ glycol dimethacrylate cross-polymer porous microspheres to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.	Ortho-McNeil Pharmaceutical Inc
Carac cream	Carac Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate / glycol dimethacrylate cross-polymer and dimethicone. Carac is a once-a-day topical prescription product for the treatment of actinic keratosis (AK), a common pre-cancerous skin condition caused by over-exposure to the sun	Dermik Laboratories, Inc. Berwyn , PA
Line eliminator dual facial treatment.	Lightweight cream with a retinol (Vitamin A) in MDS, dual-system delivers both immediate and time released wrinkle-fighting action. Visibly diminishes appearance of fine lines, wrinkles & skin	Avon

	discolorations associated with aging.	
Retinol cream, retinol 15 night cream	A night time treatment cream with Microsponge technology using a stabilized formula of pure retinol, Vitamin A. Continued use of Retinol 15 will result in the visible diminishment of fine lines and wrinkles, a noticeable improvement in the skin discolorations due to aging, and enhanced skin smoothness	Biomedic, Sothys
Epi Quin Micro	The Microsponge® system uses microscopic reservoirs that entrap hydroquinone and retinol. The microsponges release these ingredients into the skin gradually throughout the day. This provides the skin with continuous exposure to hydroquinone and retinol over time, which may minimize skin irritation. EpiQuin Micro is a prescription moisturizing fading cream that reduces the impact of these conditions known as melasma, post inflammatory hyper pigmentation or solar lentigines. Also help in Age spots, Sun spot facial discoloration.	Skin medica Inc

Sports cream RS and XS	Topical analgesic-anti-inflammatory and counterirritant actives in a Microsponge® Delivery System (MDS) for the management of muculoskeletal condition	Embil Pharmaceutical Co. Ltd
Salicylic peel 20 and 30	Deep BHA peeling agent for (professional use only): Salicylic acid 20%, Microsponge Technology, Excellent exfoliation and stimulation of the skin for more resistant skin types or for faster results. Will dramatically improve fine lines, pigmentation, and acne concerns. Salicylic Acid moves easily through the pores, clearing them out while reducing inflammation. This treatment effectively combats acne, leaving a wonderfully smooth and clear complexion.	Biophora
Micropeel plus/ acne peel	The MicroPeel Plus procedure stimulates cell turnover through the application of salicylic acid in the form of microcrystals using Microsponge ® technology. These microcrystals target the exact areas on the skin that need improvement. The Micro Peel Plus aggressively out performs other superficial chemical peels by freeing the skin	Biomedic

	of all dead cells while doing no damage to the skin.	
Oil free matte block spf20	This invisible oil-free sunscreen shields the skin from damaging UV sun rays while controlling oil production, giving you a healthy matte finish. Formulated with microsponge technology, Oil Free Matte Block absorbs oil, preventing shine without any powdery residue.	Dermalogica
Oil control lation	A feature-light lotion with technically advanced microsponges that absorb oil on the skin's surface during the day, for a matte finish. Eliminate shine for hours with this feature-weight lotion, formulated with oil-absorbing Microsponge technology. The naturally-antibiotic Skin Response Complex soothes inflammation and tightness to promote healing. Acne-Prone, oily skin conditions.	Fountain cosmetics
Lactrex ™ 12% moisturizing cream.	Lactrex™ 12% Moisturizing Cream contains 12% lactic acid as the neutral ammonium salt, ammonium lactate. Microsponge® technology has been included for comfortable application and long lasting moisturization. Lactrex™ also contains water and glycerin, a	SDR Pharmaceuticals, Inc., Andover , NJ , U.S.A. 07821

	natural humectant, to soften and help moisturize dry, flaky, cracked skin	
Dermatologica oil control lotion	A feather-light lotion containing microsponges to absorb oil on the skin's surface, helping to combat shine and maintain an all-day matte finish. Niacinamide, Zinc Gluconate, Yeast Extract, Caffeine and Biotin purify and inhibit overactive sebaceous gland activity while soothing irritation. Salicylic Acid clears congested follicles to minimize future breakout activity, while Enantia Chlorantha Bark Extract controls over-active oil glands, helping to reduce oil.	John and Ginger Dermalogica Skin Care Products
Aramis fragrances	24 Hour High Performance Antiperspirant Spray Sustained release of fragrance in the microsponge. The microsponge comes in the form of an ultra light powder, and because it is micro in size, it can absorb fragrance oil easily while maintaining a free-flowing powder characteristic where release is controlled due to moisture and temperature.	Aramis Inc.
Ultra guard	Microsponge system that contains dimethicone to help protect a baby's skin from diaper rash. The	Scott paper company.

	new wipe contains a skin protectant that helps keep wetness and irritants from the baby's skin. The solution is alcohol-free, hypoallergenic and contains dimethicone, an ingredient found in baby creams, lotions and skin protectance	

2. AIM AND OBJECTIVE

The proposed work involves formulation and evaluation of sertaconazole microsponges by using Eudragit RS100 as polymer. And finally the optimized microsponges formulation are incorporated into gel to apply on skin for the treatment of fungal infection with sustained release rate and better patient compliance.

The important objectives of the proposed research work are:-

- To study the effect of different ratio of drug:polymer on the change in physical and morphological properties, particle size and size distribution, encapsulation efficiency.
- To analyze the integrity of the drug in the microsponges by FTIR
- To incorporate optimized Microsponge formulations in gel formulation.
- To perform in-vitro drug release studies from the entire drug: polymer ratios.
- To perform the *in-vitro* drug diffusion studies of gel formulation

3. PLAN OF THE WORK

PREFORMULATION STUDIES

- Determination of Melting Point.
- Determination of Wavelength.
- Determination of Solubility.
- Determination of pH.

PREPARATION OF MICROSPONGES OF SERTACONAZOLE

- Preparation of Microsponge.
- Incorparation Of Sertaconazole Loded Microsponges In To Gel Formulation.

EVALUATION OF MICROSPONGES OF SERTACONAZOLE

- Drug Excipient Compatibility Studies.
- Determination Percentage Yield.
- Drug Loading And Drug Entrapment
- Particle Size Analysis.
- Morphology Study Using Scanning Electrone Microscope.
- *In Vitro* Dissolution Studies

EVALUATION OF SERTACONAZOLE MICROSPONGE GEL

- Visual Inspection.
- pH Measurement.
- Spreadability Studies.
- Viscosity Measurement.
- *In Vitro* Drug Release.

4. REVIEW LITERATURE

- **Kawashima *et al.*, (1989)[64]** have prepared controlled release microsphere of Ibuprofen with acrylic polymers by a novel Quasi-Emulsion Solvent-Diffusion technique and the microspheres obtained had a matrix or sponge like texture and the drug release from the microspheres could be controlled by the type and concentration of the polymer.

- **Perumal D (2001)[65]** has worked on the microencapsulation of ibuprofen. The microsphere were prepared by the emulsion solvent diffusion technique using Eudragit RS 100 as the retardant material. The influence of various process and variables like the presence/absence of baffles in the reaction vessel, agitation rate and drying time of microsphere, polymer and drug content on the microencapsulation efficiency, in vitro drug release and micrometric properties were analyzed. By increasing the agitation speed the particle size decreased. By drying the microsphere at 40+ 0.5^0C for 24hrs gave particles with less moisture content and free flowing nature. The release studies show that microencapsulation with Eudragit RS 100 gave controlled release of the drug. And 9.1% Eudragit RS 100 released the drug more rapidly, while those with 33.3% Eudragit RS 100 exhibited slower drug release profile.

- **Gonul N *et al.*,(2003)[66]** have worked on the effect of pressure and direct compression on tableting of microsponges. In this study ketoprofen was used as a model drug for systematic delivery. The ketoprofen microsponges were prepared by quasi emulsion solvent diffusion technique using Eudragit RS 100 as the polymer. The microsponges possess a unique compression property due to their matrix or sponge like structure which differed from conventional microcapsules or physical mixture. The in vitro release rate studies show that the tablets prepared with microsponges exhibited typical drug release profile characterized by Higuchi-matrix model. By applying pressure more than 3800 kg/cm^2 the drug

release was higher compared to the lower pressure which was because of the structural deformation of microsponges.

- **Mandal T K et al., (2001)[67]** have developed a method for the preparation of porous biodegradable controlled release formulation of poly (lactide/glycolide) (PLGA) containing pentamidine. Scanning electron microscopy pictures showed that these micro particles are highly porous and spherical in shape. Irrespective of the oil (corn or mineral) used in the preparation; the micro particles were all smaller tan 90nm. A change in the drug/polymer ratio did not change the particle size. The efficiency of the encapsulation was higher than 58%. In the presence of the corn oil, the efficiency of encapsulation was between 60 and 66%, where as in the presence of mineral oil, the efficiency of encapsulation was between 58 and 74%. The rate of drug release from these micro particles were very high. This significantly high rate of drug release from the PLGA micro particles was due to the porous surface of morphology.

- **Beruto T D *et al.*, (2002)[68]** have worked on the effect of water in inorganic microsponges of calcium phosphates on the porosity and permeability of composites made with polymethylmethacrylate. The inorganic powder was placed inside the polymeric matrix by polymerization technique in the aqueous mixture of the required powders. The polymeric matrix obtained was porous and act as local microsponges. The total open porosity was a function of the amount of water present, which vaporized after polymerization, leaving behind the empty spaces in the polymeric matrix. A linear relationship exists between the composites and the amount of water inside the inorganic agglomerates.

- **Comoglu T *et al.*, (2003)[69]** have prepared microsponges containing ketoprofen and Eudragit RS 100 by quasi emulsion solvent diffusion method. The effect of different mixing speeds, drug/polymer ratios, solvent/polymer ratios on the physical characteristics of microsponges as well as the in vitro release rate of the

drug from the microsponges were investigated. All the factors studies had an influence on the physical characteristics of the microsponges.

- **Baykar T *et al.*, (2003)[70]** have worked on the effect of the drug/polymer ratio on the properties of the verapamil HCL loaded microspheres. The microspheres were prepared by solvent evaporation technique using the Eudragit RS 100 as polymer. The results show that the drug release profile could be slowed down by increasing polymer amount in the formulations and the particle size, surface characteristics of microspheres and dissolution of drug could be modified through the variation of drug/polymer.

- **Sato Y *et al.*, (2004)[71]** have prepared hollow microsphere by emulsion solvent diffusion method utilizing enteric acrylic polymers co-dissolved with drug in a mixture of dichloromethane and ethanol. The in vitro release studies of five different drugs which differ I aqueous solubility's were done. The results show that the aspirin, salicylic acid and ethoxybenzamide followed higuchi equation whereas indomethacin and riboflavin release profiles does not follow the higuchi equation. It was because of increased amount of riboflavin loading than the solubility of it in the mixture dichloromethane and ethanol. The drug release profile show a initial burst release as the insoluble riboflavin crystals were released preferentially at the initial stages of the release studies.

- **Dortunc *et al.*, (2004)[72]** have worked on the preparation and in vitro evaluation of Eudragit (RS RL) microsphere containing acetazolamide. Microsphere were prepared by solvent evaporation technique using acetone/liquid paraffin system. The influence of formulation factors (stirring speed, polymer/drug ratio, type of polymer, ratio of combination of polymer) on particle size, encapsulation efficiency and in vitro characteristics of the microspheres were investigated. Mean particle size changed by changing the polymer/drug ratio or the stirring speed of the system. Although the acetazolamide release rate from Eudragit RS

microspheres were very slow and incomplete for all formulations they were fast from Eudragit RL microspheres. The combination of RS and RL polymers resulted in the slowed down release rates and was suitable for peroral administration.

- **Bogataj *et al.*, (2005)[73]** have studied the effect of various preparation temperatures (10, 25, 35 40^0C) in solvent evaporation process on Eudragit RS microsphere properties (particle size and morphology, drug content and release kinetics and drug crystal state). At 10^0C particles of irregular shape were formed, where higher temperatures gradually improve the sphericity of microspheres. The results also showed that temperature has no effect on either Ketoprofen microencapsulation efficiency or on its crystal state.

- **Orlu M *et al.*, (2006)[74]** have studied the design and the evaluation of colon specific drug delivery system containing Flurbiprofen microsponges. Microspnges containing Flurbiprofen (FLB) and Eudragit RS 100 were prepared by quasi-emulsion solvent diffusion method. Additionally FLB was entrapped into a commercial Microsponges® 5640 system using entrapment method. Afterwards, the effect of drug/polymer ratio, inner phase solvent amount, stirring time and speed and stirrer type on the physical characteristics of microsponges were investigated. The thermal behavior, surface morphology, particle size and pore structure of microsponges were examined. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin: Hydroxypropylmethyl Cellulose (HPMC) mixture followed by tableting. It was concluded that both the microsponges prepared by quasi-emulsion solvent diffusion method and Microsponge® 5640 can be used successfully in the systems designed for colon specific drug delivery.

- **Yan Gao *et al.*, (2006)[75]** have prepared microspheres of Roxithromycin with Eudragit RS 100 ad silica by the emulsion solvent diffusion method to mask the bitter taste of the antibiotic. The effect of different polymers and drug/polymer

ratios on the taste masking and the characteristics of the microspheres were investigated. It was found that Eudragit RS 100 was the best for masking the unpleasant taste of Roxithromycin among the six kinds of polymers investigated. The influence of other formulation factors, i.e. dichloromethane-acetone ratios and silica-polymer ratios on the properties of the microspheres were also examined. In conclusion, the results of the present study will be helpful for the preparation of oral forms of Roxithromycin with an acceptable taste.

- **Chen G *et al.*, (2005)[76]** have worked on the culturing of skin fibroblast in a thin PLGA-collagen hybrid mesh. The hybrid mesh was constructed by forming web-like collagen microsponges in the openings of a PLGA knitted mesh. The results indicate that the web-like collagen microsponges formed in the openings of the PLGA Knitted mesh increase the efficiency of cell seeding, improved cell distribution, and therefore facilitated rapid formation of dermal tissue having a uniform thickness. PLGA collagen microsponges are useful in the skin tissue engineering.

- **Cevher E *et al.*, (2006)[77]** have worked on the design and evaluation of colon specific drug delivery system containing Flurbiprofen microsponges. Flurbiprofen (FLB) microsponges were prepared by quasi emulsion solvent diffusion techniques using Eudragit RS 100 as polymer. The effect of drug/polymer ratio, inner phase volume, stirring time and rate, on physical properties of the microsponges were determined. The results show that the microsponges were of spherical shape with spherical and cylindrical hole like pores. The plastic properties of microsponges allow direct compression of the microsponges to obtain mechanically strong tablets than the physical mixture of drug and polymer. The I vitro release profile shows that the drug release from the microsponges was faster than compared to the rigid micro particles due to more porous internal structure of microsponges.

- **Jelvehgari M *et al.*, *(*2007)[78]** have worked on the preparation, characterization and release studies of Benzyle Peroxide microsponges. The effect of drug/polymer ratio on topography, particle size and distribution and porosity were analyzed. According to the results, the topographical study shows that the micro particles obtained were spherical and contain interconnected pores (appearing like a sponge); with increase in drug/polymer concentration the mean particle size of the sponges decreased.. The drug release studies were done by formulating BPO microsponges as a cream. The release shows that as the drug/polymer ratio increases the release of drug from BPO microsponge cream was reduces because of the decreased internal porosity of the microsponges with increase in drug/polymer.

- **Nokhodchi A *et al.*, (2007)[79]** have worked on the factors affecting the morphology of BPO microsponges. BPO microsponges were prepared using an emulsion solvent diffusion method by adding an organic internal phase containing BPO, ethyl cellulose and dichloromethane (DCM) into a stirred aqueous phase containing polyvinyl alcohol (PVA) with stirring for about 8hrs until complete diffusion of DCM. The results shows that the microsponges obtained by this techniques were predominantly of spherical shape and contain orifices with sponge like appearance. The effect of drug/polymer ratios on morphology, particle size and size distribution were determined; with increase in drug/polymer concentration the porosity and the mean particle size size of the sponges decreased. The prepared microsponges were formulated as lotions and the drug release was performed. The data show that an increase in drug/polymer ratio resulted in a reduction in the release rate of drug from BPO microsponge lotions, due to decreased internal porosity of the microsponges.

- **Wester RC *et al.*, (1991)[80]** have revealed that the controlled release of BPO from a porous microsphere polymeric system can reduce topical irritancy. The controlled release of BPO to skin can alter the dose relation that exists between

efficacy and skin irritation. Corresponding studies showed reduced skin irritation in cumulative irritancy studies in rabbits and human beings, where as in vivo human antimicrobial efficacy studies showed that application of the formulations containing entrapped BPO significantly reduced counts of Propioni bacterium acnes (p less than 0.001) and aerobic bacteria (p less than 0.001) and the free fatty acid/triglyceride ratio in skin lipids. These findings supports the hypothesis that, at least for this drug, controlled topical delivery can enhance safety without sacrificing efficacy.

- **Netal Amrutiya *et al.*, (2009)[81]** have worked on development of microsponges for topical delivery of Mupirocin and they prepared microsponges containing Mupirocin by an emulsion solvent diffusion method. The effect of formulation and the process variables such as internal phase volume and stirring speed on the physical characteristics of microsponges were examined on optimized drug/polymer ratio 3^2 factorial design. The optimized microsponges were incorporated into an emulgel base. In vitro drug releases, ex vivo drug deposition, and in vivo antibacterial activity of mupirocin-loaded formulations were studied. And they have concluded that, the formulations showed enhanced retention of drug in skin, indicating better potential of delivery system as compared with marketed mupirocin ointment and conventional Mupirocin emulgel.

- **Ferhan Sevgi *et al.*, (2009)[82]** have worked on formulation, in vitro release and in situ studies in rats of mefenamic acid micro particles and they prepared mefenamic acid loaded Chitosan and alginate beads by Ionotropic gelation process and microsponges containing mefenamic acid and Eudragit RS 100 by quasi emulsion solvent diffusion method and they investigated the in vitro characteristics of mefenamic acid micro particles as well as their effects on DNA damage.

- **Vikas Jain *et al.*, (2009)[83]** have worked on development and characterization of Eudragit RS 100 loaded microsponges and its colonic delivery using natural

Polysaccharides. Paracetamol loaded Eudragit based microsponges were prepared using quasi-emulsion solvent diffusion method. The compatibility of the drug with various formulation components was established. Process parameters were analyzed in order to optimize the formulation. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. The colon specific formulations were prepared by compression coating of microsponges with pectin: hydroxymethylcelllulose (HPMC) mixture followed by tableting. The in vitro dissolution studies were done on all formulations and the results were evaluated kinetically and statically. And concluded that the prepared microsponges exhibited characteristics of an ideal delivery system for colon targeting. The unique compressibility of microsponges offers a new alternative for producing mechanically strong tablets. Further colon specific tablets based on microsponges could prevent effective local action ad microsponges may selectively be taken up by the macrophages present in colon.

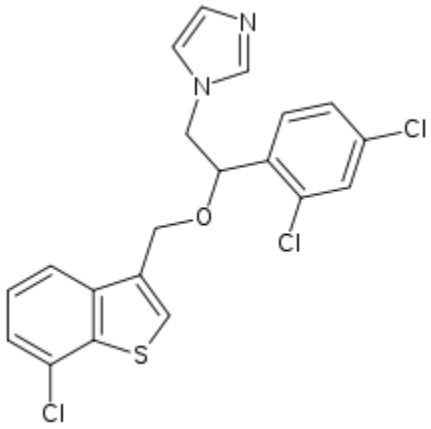
- **Yan yang *et al.*, (2009)[83]** have worked on development of highly porous large PLGA micro particles for pulmonary drug delivery. They introduced a new process of making highly porous large polymeric micro particles for local drug delivery to the lungs by inhalation. Poly (lactic-co-glycolic acid) (PLGA) micro particles (average diameter, 10-20mm) were prepared by the double-emulsion method, in which PLGA was dissolved in dichloromethane. Freshly prepared Ammonium Bicarbonate solution (1% or 1.5%) was added to the polymer solution, and the mixture was sonicated in ice bath. The sonicated mixture was added to 1% polyvinyl alcohol (PVA) solution while it was being homogenized at a rate ot 2000-6000 rpm for 1min, then poured into water, and stirred overnight at room temperature to remove dichloromethane. The particles were collected by centrifugation at 4000 rpm for 5min, washed 3 times with distilled water, and filtered through wet-sieve and dried.

- **Vikas jain et al,(2010)[84]** Have prepared eudragit based microsponge with potential for colonic delivery they have choosan dicyclomine as a model drug .invitro dissolution study showed that increased drug : polymer resulted in reduction from the microsponge drug release was biphasic with an initial effect with 16-30% of drug was released in the first 1 hr.cumulative release for the microsponges over 8 hrs ranged from 59-86%.

- **Katarzyna winnicka et al,(2012)[84]** Investigated the inflence of PAMAM NH2 of PAMAM-OH dendrimers generation 2 and 3 generation on the soulbility and antifungal activity of ketoconazole and to design and evaluate ketoconazole hydrogel of PAMAM dendrimers.the antifungal activity of designed ketoconazole with PAMAM NH2 dendrimers measured by the plate diffusion method was definitely higher than the pure ketoconazole hydrogel and also as compared to commercially available product.

5. DRUG PROFILE

Chemical structure of Sertaconazole[85]



Description: Sertaconazole is a antifungal medication of the imidazole class. It is avoidable as a cream to treat skin infection such as athlete's foot.

Chemical formula: $C_{20}H_{15}Cl_3N_2OS$

IUPAC Name: 1-{2-[(7-chloro-1-benzothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1H-imidazole

Therapeutic efficacy

In randomized, double-blind, multicentre trials of 3–6 weeks' duration (n=127-383), a significantly greater number of patients with tinea of the glabrous skin and tinea pedis receiving a topical 2% sertaconazole cream once or twice daily achieved a successful mycological cure copmared with recipients of a placebo cream. Sertaconazole, a topical azole antifungal agent, exhibits a dual antifungal mechanism of action, antibacterial activity, and antiinflammatory properties and demonstrates a broad spectrum of activities against numerous fungal pathogens. Topical Sertaconazole is efficacious and safe in the treatment of cutaneous dermatophytosis, tinea versicolor (pityriasis versicolor), cutaneous candidiasis, intertrigo and seborric dermatitis. Pharma-kinetic properties demonstrates an epidermal reservoir effect post treatment. Sertaconazole has proven to be both safe and well tolerated, based on available data worldwide.

Sertaconazole 2% cream is the most recently introduced topical azole antifungal agent in the united states indicated for treatment of tinea pedis[86,87].

Mechanism of action:

Similar to other azole antifungal agents, Sertaconazole inhibits lanosterol 14-alpha demethylis resulting in subsequent reduction in synthesis of ergosterol, the primary sterol contributing to fungal cell membrane function and stability[88, 89]. The decreased availability or ergosterol coupled with intracellular accumulation of 14-alpha-methylesterols leads to increased membrane rigidity, alteration in membrane permeability changes in important membrane bound enzymes growth inhibition and ultimately death of fungal cells[90,91]. In addition it has been reported that Sertaconazole induces direct damage to memmbranes of susceptible organism through binding to non sterol lipids resulting in impaired mmembrane regulatory function, leakage or intracellular contents such as adenosine triphosphate and rapid cell death. Sertaconazole also has been shown to exhibit anti-inflammatory activity and anti-bacterial activity against some staphylococci and streptococci[92].

Anti-inflammatory property:

The anti-inflammatory properties of several antifungal agents including miconazole, fluconazole, Sertaconazole, terconazole, ketoconazole and ciclopirox where studies in multiple invivo and inviitro preclinical models of cutaneous inflammation and pruritus with Sertaconazole exhibiting the greatest ability to suppress cytokine release from phytohemagglutinin-stemulated human peripheral blood lymphocytes[93]. It has also been reported that Sertaconazole was superior to other tested azole antifungal agents including ketoconazole in reducing irritant dermatitis in an year edema model and that it reduced scratching response in a murin model of pruritus comparable to hydrocortisone[94]. The anti- inflammatory properties of antifungal agents such as Sertaconazole are believed to be important in symptom reduction especially early in the course of treatment and may obviate the need for application of other topical antipruritic agents.

Pharmacokinetic properties:

The lipophilicity of Sertaconazole related to its synthesis with a lipophilic benzothiophene ether is believed to Contribute to enhancement of epidermal penetration after topical application, with negligible systemic absorption noted on plasma analysis[95]. A cutaneous reservoir affect has been noted, with 72% of the applied dose of Sertaconazole present at 24Hrs after application and with a cutaneous retention time test demonstrating the superior antifungal effect of Sertaconazole at 12, 24, and 48Hrs after application compared with that of bifonazole. Although approved product labelling for Sertaconazole Nitrate 2% cream in the United States indicates an application frequency of twice daily, the persistence of antifungal activity after application and the cutaneous reservoir affect explain why this agent has been shown to be effective after application once daily.

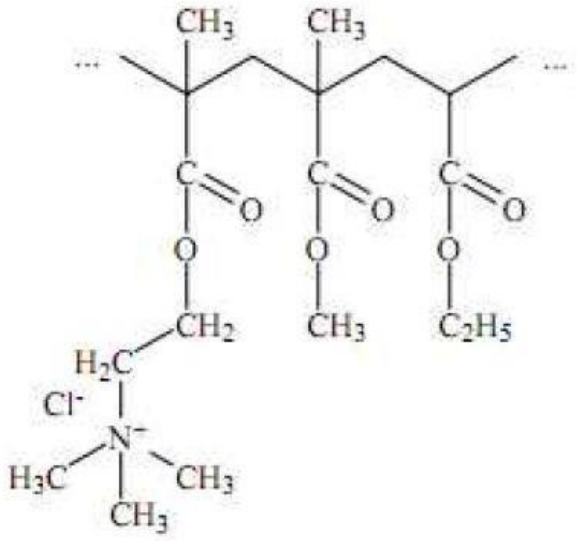
Spectrum of Activity

Sertaconazole has been shown to be active against dermatophytes, including T rubrum, T mentagrophytes, and E floccosum; yeasts, including C albicans, C glabrata, C krusei, Candidaparapsilosis, C trophicalis, and M furfur; and some gram positive bacteria, including staphylococcal and streptococcal organisms. The antifungal activities of Sertaconazole against fungal isolates known to cause superficial fungal infection has been shown to be comparable or superior to that of other topical antifungal agents, including bifonazole and terpinafine[96,97].

Eudragit RS100[98]

Chemical name: poly (ethyl acrylate-co-methyl methacrylate co-trimethylamino ethyl methacrylatechloride)

Chemical structure:



Molecular weight: 32000g/mol

Description: Colourless, clear to cloudy granules with a faint amine like odor .

Solubility: 1g of the substances dissolves in aqueous methanol ethanol and isopropyl alcohol as well as in acetone ethyl acetate and methylene chloride to give clear to cloudy solution the substances are practically insoluble in petroleum ether 1N sodium hydroxide and water.

Product form: Granules

Targeted drug release area: Time controlled release, pH independent.

Drug Substance/Residue on evaporation : 1g of the polymer is dried in an oven for 5hr in vaccum at 80^{o}C. Not less than 97%.

Loss on drying: Max.3.0%according to "dry substance/residue on evaporation.

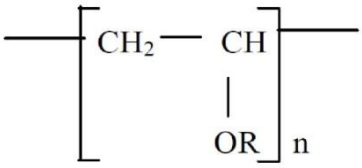
Storage: Protect from light temperature and moisture. Storage at any temperature between 8^0C and 25^0C fulfils this require ment.

Stability : The product is required minimum stability datas are given on their labels and batch related analysis for certificates.

POLYVINYL ALCOHOL (PVA)[98]

Chemical Name**:** Ethanol Homopolymer

Chemical Structure:



where R = H or $COCH_3$

Description: Odorless, translucent, white or cream-colored granular powder.

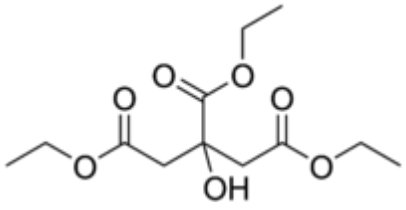
Solubility: Soluble in water, sparingly soluble in ethanol.

Uses: Coating, binder, sealing agent and surface-finishing agent.

TRIETHYL CITRATE[98]

Chemical Name: 1,2,3-Triethyl 2-hydroxypropane-1,2,3-trycarboxylate

Chemical Structure:

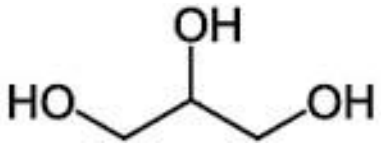


Molecular Weight: 276.283 g/mol.

Appearance: Oily Liquid.

Uses: Tryethyl Citrate is used in pharmaceutical coatings and plastics. It is also used as a plasticizer for polyvinylchloride and similar plastics.

GLYCEROL[98]



Description: Glycerol is a clear, colorless, odorless, viscous, hydroscopic liquid. It has a sweet taste.

Molecular Formula: $C_6H_8O_3$

Molecular Weight: 92.09

Melting Point: 17.8°C

Boiling Point: 290°C

Hydroscopicity: Hydroscopic

Density: 1.2636 g/cm^3 at 20°C

Solubility: Slightly soluble in acetone, practically insoluble in benzene, chloroform, oil, soluble in ethanol (95%), methanol, and water.

Incompatibilities: with strong oxidizing agent.

Functional Category: Antimicrobial preservative, emollient, humectants.

6. MATERIALS AND METHODS

Table: 3

List of Chemicals

Sl. No:	Material	Supplier
1	Sertaconazole	Royal Pharm, Hanghou (China)
2	Eudragit RS100	Degussa India Pvt. Ltd, Mumbai
3	Triethyl Citrate	Sigma Aldrich Pvt. Ltd, Mumbai
4	Poly Vinyl Alcohol	Loba Chemical Pvt. Ltd, Mumbai
5	Ethyl Alcohol	Changshu Yangyuan Chemical, China.
6	Carbopol 940	Yaro Chem Pvt. Ltd, Mumbai
7	Triethanolamine	Nice Chemicals, Cochin
8	Methyl Paraben	Nice Chemicals, Cochin
9	Propyl Paraben	Nice Chemicals, Cochin
10	Sodium Hydroxide	Rankem, Gurgaon
11	Potassium Hrydrogen Phosphate	Nice Chemicals, Cochin

Table: 4

List of Equipment‟s & Instruments used

Sl. No:	Name	Manufacturer
1	Homogenizer – Stirrer	Remi Motors, Mumbai
2	Magnetic – Stirrer	Remi Motors, Mumbai
3	Ultra Sonicator	Serve well instrument Pvt.Ltd,Banglore
4	Hot Air Oven	Techno Scientific Products
5	Electronic Weighing Balance	BEL Engineering
6	UV/Visible Spectrophotometer	Shimanduz, Japan UV-1700
7	Franz Diffusion Cell	LabECX
8	Digital pH Meter	Labtronics Model LT-10
9	Melting Point Apparatus	Labtronics
10	FT-IR Spectrometer	Shimanduz, Japan IR Affinity – 1

6. METHODS

6.1PREPARATION OF CALIBRATION CURVE OF SERTACONAZOLE IN PHOSPHATE BUFFER pH4

6.1.1 Preparation of standard stock solution of sertaconazole in phosphate buffer pH4

6.1.2 Preparation of calibration curve of sertaconazole.

6.2PREFORMULATION STUDIES.

6.2.1 Determination of melting point.

6.2.2 Determination of wave length.

6.2.3 Determination of solubility.

6.2.4 Determination of pH.

6.3 PREPARATION OF MICROSPONGES OF SERTACONAZOLE .

6.3.1 Preparation of microsponge.

6.3.2 Incorparation of sertaconazole microsponges in to gel formulation.

6.4 EVALUATION OF MICROSPONGES OF SERTACONAZOLE

6.4.1 Drug-Excipient Compatibility Studies.

6.4.2 Determination Percentage Yield.

6.4.3 Drug Loading And Drug Entrapment

6.4.4 Particle Size Analysis.

6.4.5 Morphology Study Using Scanning Electrone Microscope.

6.4.6 In Vitro Dissolution Studies

6.5 EVALUATION OF SERTACONAZOLE MICROSPONGE GEL

6.5.1 Visual Inspection.

6.5.2 pH Measurement.

6.5.3 Spreadability Studies.

6.5.4 Viscosity Measurement.

6.5.5 In Vitro Drug Release.

6.1 PREPARATION OF CALIBRATION CURVE OF SERTACONAZOLE IN PHOSPHATE BUFFER pH 4.0

6.1.1 Scanningof standard stock solution of sertaconazole in phosphate bufferpH 4.0

The solution containing 30µg/ mL of sertaconazole in phosphate buffer pH 4.0 was prepared and scanned over the range of 200-400 nm against phosphate buffer pH 4.0 as a blank using Shimadzu UV/Visible double beam spectrophotometer. The solution exhibited UV maxima at 260 nm [99].

6.1.2 Preparation of standard calibration curve in phosphate buffer pH 4.0

Accurately weighed 10 mg of sertaconazole was transferred to a 100 mL volumetric flask and dissolved in sufficient quantity of phosphate buffer pH 4.0. The volume was adjusted to the mark with phosphate buffer pH 4.0 to prepared stock solution of 100 µg/ mL. From the stock solution aliquots of working solution of sertaconazole were transferred in to a series of 10 mL volumetric flask and made volume up to mark with phosphate buffer pH 4.0. The absorbance of resulting solution was measured at 260 nm against blank solution prepared similarly without drug using Shimadzu UV/Visible double beam spectrophotometer. The standard curve is generated using Microsoft excel 2007 by plotting concentration verses absorbance. The experiment was performed in triplicate and average values with standard deviation were reported. The method obeys Beer-Lambert's law in concentration range of 5-30 µg/ mL.

6.2 PREFORMULATION STUDIES[99]

Preformulation test is the first step in rational developments of dosage forms of a drug substance. Pre formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed on

the obtained sample of drug for identification and compatibility studies. The following preformulaton studies were performed for sertaconazole.

6.2.1 Determination of Melting Point.

Melting point of drug was determinted by capillary tube method, by taking small amount of drug in a capillary tube, in which the other end is closed. The capillary tube was placed in a melting point apparatus and the temperature at which the drug melt was recorded. The procedure was repeated thrice to get average value.

6.2.2 Determination of Solubility

Solubility is one of the important consideration in formulation. The solubility test in various solvents such as distilled water, methanol, ether, alcohol, methelene chloride were estimated.

6.2.3 Determination Of pH

The determination is carried out at a temperature of $25^0C \pm 2$, unless otherwise specified in the monograph. The pH value of the solution is determined potentiometry.

6.3 PREPARATION OF MICROSPONGES OF SERTACONAZOLE[100].

6.3.1 Preparation of Microsponges

Microsponges were prepared by the quasi emulsification solvent diffusion method.

Inner phase: It is prepared by dissolving the Eudragit RS100 in ethanol. The drug was added to the solution and dissolved under ultra-sonication at 35ºC for 15mins.

Outer phase: Dissolving PVA in distilled water and the process was carried out at room temperature, then the inner phase was poured into outer phase ta room temperature. After emulsification, the mixture was continuously stirred at 500rpm for 2Hrs. After the formation of Microsponges, the mixture is filtered to separate the Microsponges. The product was washed and dried in oven at 40ºC. For the evaluation of the Drug: Polymer ratio on the

physical characteristics of Microsponges. Seven different weighing ratio of drug to Eudragit RS100 are 1:1, 1:2, 1:3, 1:4, 1:5, 1:6 and 1:7.

Table: 5

Composition of Sertaconazole Microsponges Formulation

Formulation Code	Drug : Polymer	Drug (g)	Polymer (g)	Eudragit RS100	Ethanol (ml)	Glycerol (ml)	Water (ml)	PVA (g)	Stirring Rate (rpm)	Stirring Time (Hrs.)
F1	1:1	0.2	0.2	RS100	10	1	200	0.4	500	2
F2	1:2	0.2	0.4	RS100	10	1	200	0.4	500	2
F3	1:3	0.2	0.6	RS100	10	1	200	0.4	500	2
F4	1:4	0.2	0.8	RS100	10	1	200	0.4	500	2
F5	1:5	0.2	1.0	RS100	10	1	200	0.4	500	2
F6	1:6	0.2	1.2	RS100	10	1	200	0.4	500	2
F7	1:7	0.2	1.4	RS100	10	1	200	0.4	500	2

Table: 6

Optimum values for Microsponges

Drug Polymer ratio	1:1, 1:2, 1:3 etc.
Amount of drug	2gm
PVA	30 – 70mg
Inner phase solvent	Ethyl Alcohol
Amount of inner phase solvent	10ml
Amount of water in outer phase	200ml
Temperature of inner phase	37^{o}C
Stirring rate	500rpm
Stirring time	60mins

6.3.2 Incorporation of Sertaconazole loaded Microsponges into gel formulation

Sertaconazole Microsponge gel was prepared by using following formula given in the below table. A clear dispersion of carbopol was prepared in water using moderate agitation.

- A clear dispersion of carbopol (35mg) is prepared in water (q.s) using moderate agitation.
- Triethanolamine (1-2 drops) is used to neutralize the formulation and subsequently preservatives Methyl Paraben (3mg) and Propyl Paraben (1mg) was added to resist the microbial growth.
- And then volume was maintained with water. Gel prepared were degassed with ultra sonication.

Table: 7

Table revealing the master formula for gel formulation

S. No.	Ingredient	Quantity (mg/ml)
1	Carbopol 940	35
2	Triethanolamine	2
3	Methyl Paraben	3
4	Propyl Paraben	1
5	Distilled Water	q.s

6.4 EVALUATION OF MICROSPONGES OF SERTACONAZOLE[101]

6.4.1 Drug Excipient Compatibility Studies Using FT-IR

The compatibility study of sertaconazole with other excipients was done by using Fourier transform infrared spectroscopy (FT-IR). FT-IR spectra of pure drug and mixture of drug and other excipients were measured using FT-IR instrument using KBr method. The samples to be tested were mixed with solid potassium bromide (KBr). The mixture was then pressed into a very thin pellet. The pellets were placed in the holder directly in the IR laser beam. Spectra were recorded using Shimadzu FTIR- 8400s loaded with IR

solution version 1.2 software. The FT-IR spectrum of physical mixture was compared with the standard FT-IR spectrum of the pure drug for any major interaction. Each spectrum was recorded in the frequency range of 3800-600cm^{-1} IR spectra of sertaconazole ,Eudragit RS 100, physical mixture of both and microsponge formulation of sertaconazole and Eudragit RS 100 were done using FTIR spectrometry.

6.4.2 Determination of Percentage Yield

The prepared microsponges of all batches were accurately weighed. The measured weight of prepared microsponges was divided by the total amount of all the excipients and drug used in the preparation of the microsponges, which give the total percentage yield of floating microsponges. It was calculated by following equation,

$$\% \text{ Yield} = \frac{\text{Practicle yield}}{\text{Therotical yield(excipient+sdrug)}} \times 100$$

6.4.3 Drug Loading and Drug Entrapment

Microsponges equivalent to 100mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by dissolving with 100ml 7.4 phosphate buffer solution with the aid of sonication. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, japan) at 260 nm against appropriate blank. The amount of drug loaded and entrapped in the microsponges was calculated by the following formulas:

$$\% \text{ Drug Loading} = \frac{\text{Weight of the drug loaded in the microsponges (DC)}}{\text{Total weight of the microsponges}} \times 100$$

$$\% \text{ Encapsulation efficiency} = \frac{\text{Amount of drug actually present (DC)}}{\text{Theoretical drug load expected}} \times 100$$

(DC = Actual Drug Content)

6.4.4. Particle size analysis

Determination of average particle size of sertaconazole microsponge was determined by an optical microscope using caliberation ocular and stage micrometer under regular polarized light. A minute quantity of microsponge spread on clean glass slide and the average particle size was calculated by measuring 100 particle of each batch.

6.4.5 Morphology Study Using Scanning Electrone Microscope

The internal and external morphology and surface topography can be studied by scanning electron microscopy (SEM). Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then SEM images of microsponges were recorded at the required magnification. SEM of a fractured microsponge particle can also be taken to illustrate its ultra structure.

6.4.6 *In Vitro* Dissolution Studies

Dissolution profile of microsponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5μm stainless steel mesh. The speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical methods at various intravels.

6.5 EVALUATION OF SERTACONAZOLE MICROSPONGE GEL[102]

6.5.1Visual Inspection

The organoleptic properties such as color, texture, consistency, homogeneity and physical appearance of gel containing microsponges were checked by visual observation.

6.5.2 pH Measurement

Diverse gel formulation pH was recorded using digital pH meter. 5g gel was dispersed in 45ml distilled water at 27^0c and solution pH was measured.

6.5.3 Spreadability Studies

Spreadability of sertaconazole microsponge gel was measured in terms of diameter of gel circle produced when placed between two glass plates of definite weight. A weighed quantity 0.5 gm gel was placed within a circle of 1cm diameter premarked on a glass plate over which a second glass plate was placed. A weight of 500 gm was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to spreading of the gels was noted.(diameter of the spread circle – initial diameter).

6.5.4 Viscosity Measurement

The viscosity of gel formulation was determined. The viscosity was determined using a Brookfield digital viscometer (DV-E model). The sample holder taken for the viscosity measurement was filled with the samples and then inserted into a flow jacket mounted on the viscometer. The samples adaptor (spindle), rotated at an optimum speed was used to measure the viscosity of the preparation.

6.5.5 Drug content.

One gram of microsponges loaded gel was accurately weighed and dissolved in phosphate buffer pH 4.0 filterd and volume was made up to 100ml with buffer solution. The drug content was determined by diluting the resulting solution for 10 times with phosphate buffer and measuring the absorbance at 260nm using UV spectrophotometer.

6.5.6 In-Vitro Drug Release

In-vitro permeation studies using cellophane membrane

The in-vitro release of microsponges containing Sertaconazole from the gel formulation was studied through cellophane membrane using modified apparatus. The dissolution medium used was freashly prepared phosphate buffer pH 4.0. Cellophane membrane previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both end). 100 mg equivalent gel formulation of sertaconazole microsponges was kept in donor compartment. The cylinder was attached to stand and suspended in 200ml of dissolution medium maintained at 37±1^{o}C. The membrane just touching the receptor medium

surfaces. The dissolution medium was stirred at 100rpm speed using Teflon coated magnetic bead. Aliquots, each of 2ml volume were withdrawn periodically at predetermined time interval of 30, 60, 120, 180, 240,300, 360, 420,480, 540, 600min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analysed by UV-Visible spectrometer at 260nm using phthalate buffer as blank.

Kinetic modelling of *in- vitro* drug release.

The data obtained from *in vitro* release studies of best two formulations were fitted to

various models such as zero order, first order, Higuchi and Korsmeyer Peppas to obtain the

kinetic modeling of drug release.

To study the release kinetics the data obtained from *in-vitro* drug release studies were plotted in various kinetic models.

1. **Zero order rate kinetics:** %Cum.Drug Release Vs Time
2. **First order rate kinetics:** Log cum. % of drug remaining vs time.
3. **Higuchi model**: Cum. percentage of drug released vs square root of time.
4. **Korsmeyer Peppas model:** Log cumulative % of drug release vs log time.

The plots were drawn using graph pad prism version 5 and the regression equations were obtained for each plot. The correlation coefficient value (r^2) of the plot was obtained. The model with the highest correlation coefficient value (r^2approches unity) was chosen as the best fit kinetic model.

1. **Zero order kinetics**

   A zero order release can be predicted by using the equation:

   $Q^t = Q^0 – K^{0t}$

   Where,

   Q^0 = initial amount of drug present in solution (most cases $Q^0=0$)

   Q^t = the amount of drug release at time t.

   K^0 = the zero order release rate constant.

A graph of cumulative percentage of drug release vs time yields a straight line with a slope equals to K^0.

2. **First order kinetics**

The first kinetics describes the release from a system where the release rate is concentration dependent. It can be described by the following equation:

$\ln Q = \ln Q^0 - K_t^1$ Where, K_1 = first order release constant.

3. **Higuchi model kinetic**

The drug release can be predicted by the following equation:

$Q = K_t^{1/2}$

Where, K is Higuchi dissolution constant.

t is the time in hrs

The model predicts that the drug release from the dosage form is directly proportional to the square root of time.

4. **KorsmeyerPeppas model**

To evaluate drug release mechanism of drug, the in-vitro release data was plotted in Korsmeyer equation as log cumulative percentage of drug release vs log time and exponent n was calculated through slope of the straight line.

Korsmeyer equation as follows:

$Mt/M = K_{tn}$

Where,

Mt/M^{α} the fractional solute release

t = the release time

K = the kinetic constant

n is an exponent which indicates the mechanism of drug release. In the present study the limits considered were n= 0.45 indicates a classical Fickian diffusion controlled release and n=0.89 indicates a case II relaxation release transport; nonfickian, zero order release value of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the

polymer relaxation) commonly called anomalous transport. After the value reaches 0.89 and above the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order.

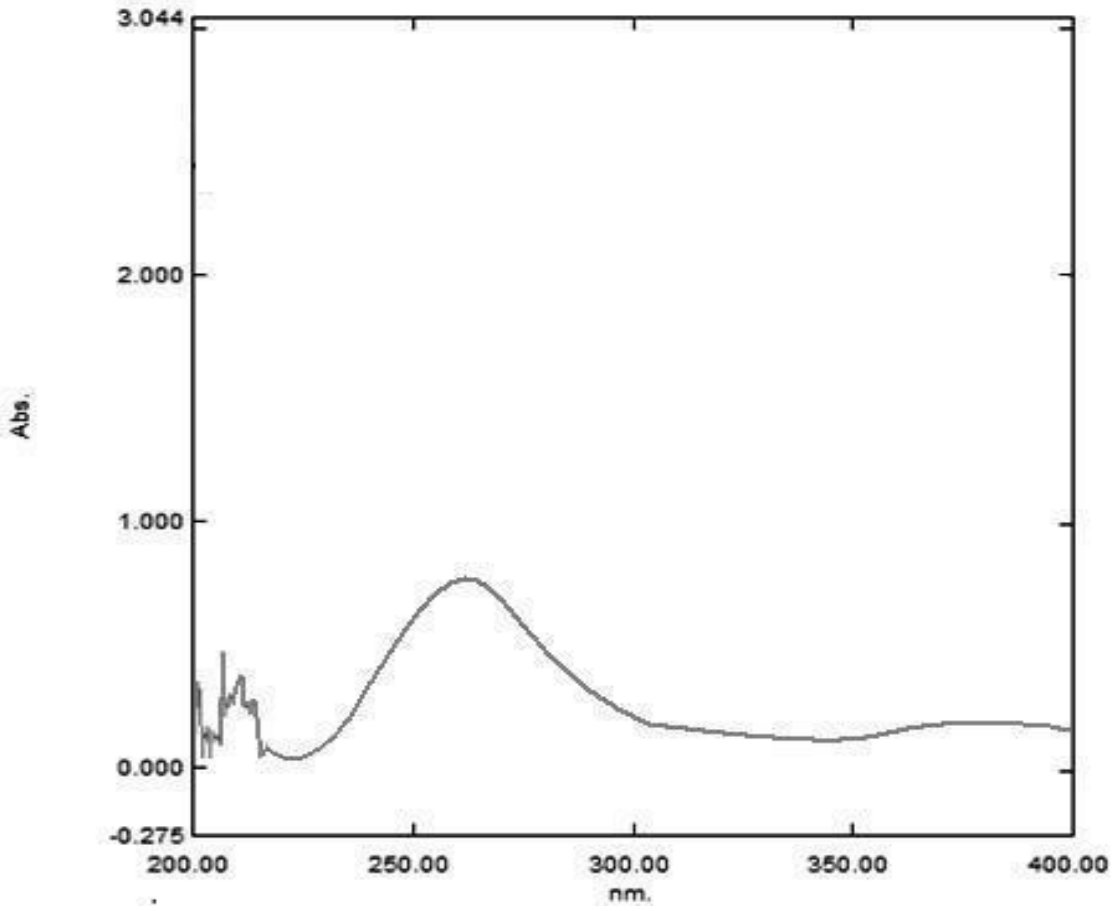
Values of „n“	**Mechanism**
0.5	Fickian diffusion (higuchi matrix)
0.5< n<1.0	Anamolous transpot
1	Case-II Transport(zero order)
n>1	Super case-II transport

7. RESULT

Analytical method

Figure: 7.1

Determination Of λ max of Sertaconazole in pH 4.0 Phosphate Buffer Solution



RESULT

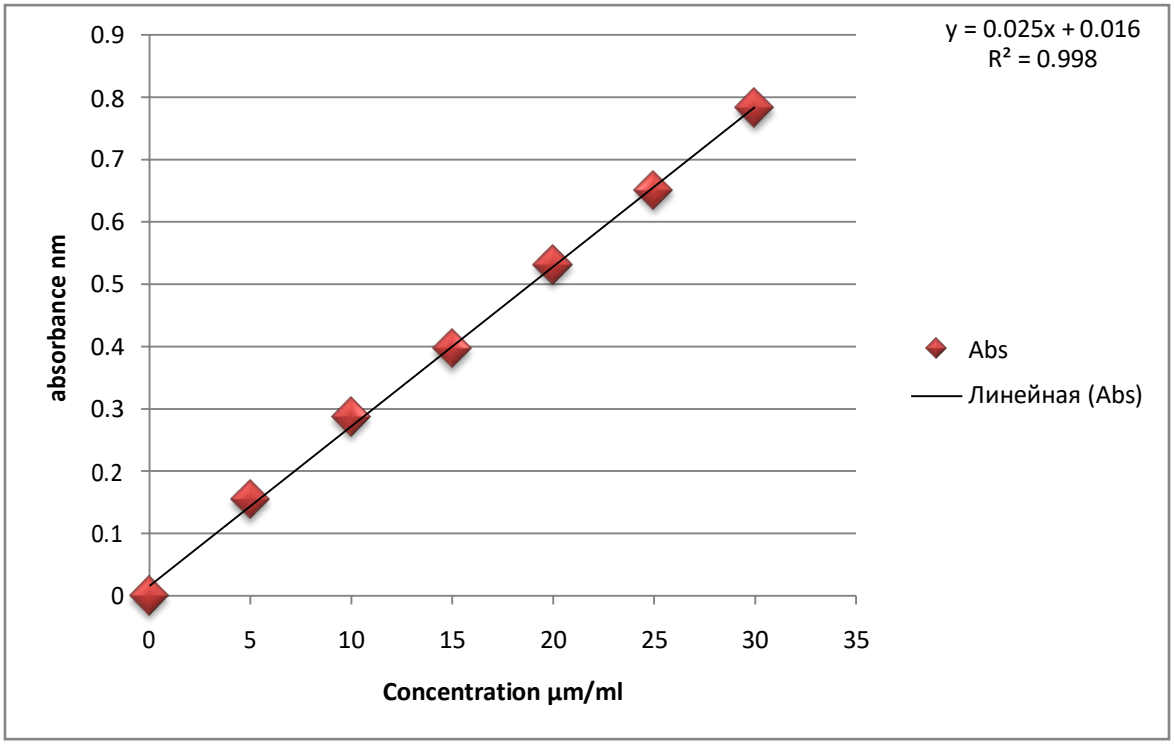
UV spectra of sertaconazole possess a common λmax at 260nm. This λmax is used for further study.

Table:8

Calibration curve of sertaconazole at pH 4.0 buffer solution

S.No.	Concentration	Absorbance at 260 nm
1	5	0.154
2	10	0.287
3	15	0.396
4	20	0.531
5	25	0.650
6	30	0.782

Figure: 7.2



Result:

The standard curve of sertaconazole was prepared in pH.4.0 phosphate buffer, the r^2 value was found to be 0.9986, which shows a linearity of absorbance between 15-35µg/ml.

PREFORMULATION STUDIES

Table: 9 Preformulation studies

The following preformulation studies were performed for sertaconazole.

Melting point	146± 1.23°C
Solubility	Practically insoluble in water, soluble in methanol, sparingly soluble in alcohol and methelene chloride.
pH	6
λmax	260nm
Colour	White or almost white powder

RESULT

The preformulation studies for the drug was conducted. The λmax of sertaconazole was found at 260nm. By determining the organoleptic poperties, it was observed that the drug was found to be white colour, and odourless. Solubility study showed that sertaconazole is practically insoluble in water, soluble in methanol, sparingly soluble in alcohol and methelene chloride. The melting point was found at 146°C.

Drug-Excipient Compatibility Studies

Preformulation studies were carried out to study the compatibility of pure drug Sertaconazole with the other excipient. The individual IR spectra of the pure drug and other excipient as well as the combination spectra of the drug and polymer are shown in the Figure: 11 which indicates no interaction between sertaconazole and other excipient when compared with infrared spectrum of pure drug as all functional group frequencies were present.

Figure: 7.3 FTIR of Eudragit RS 100

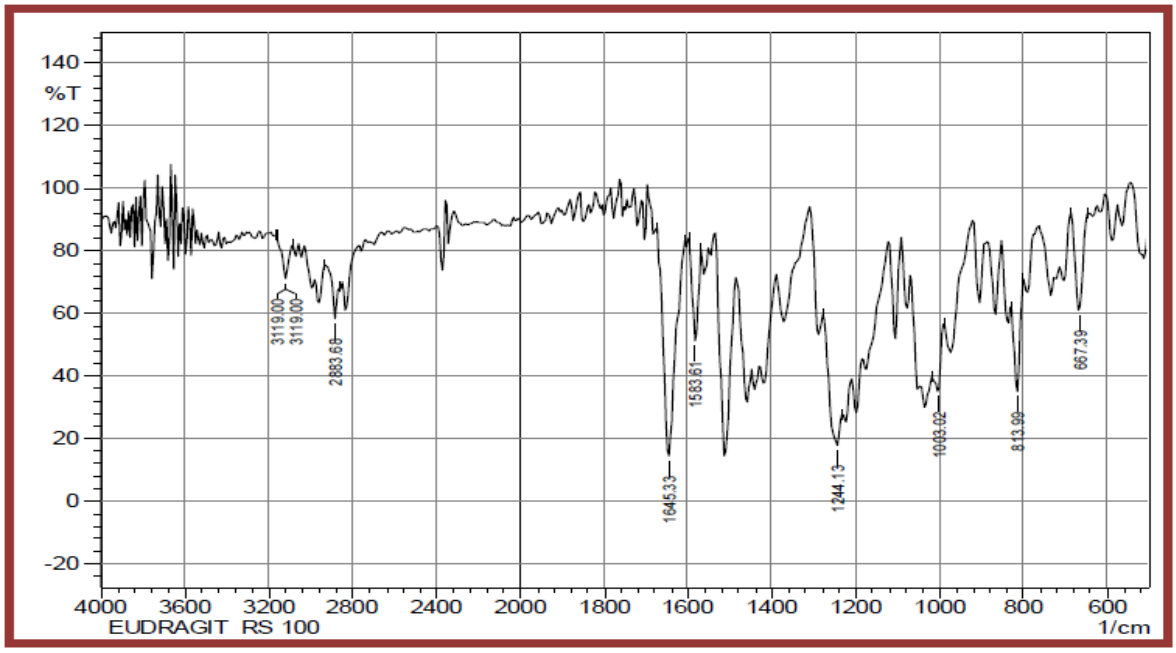


Figure: 7.4 FTIR spectra of Sertaconazole

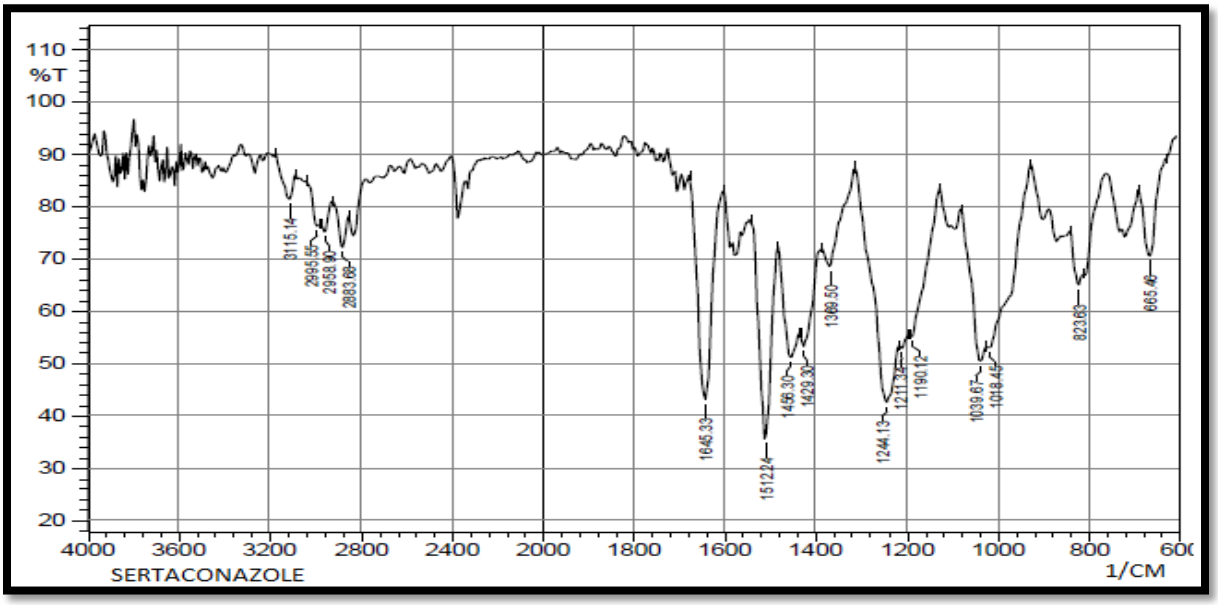
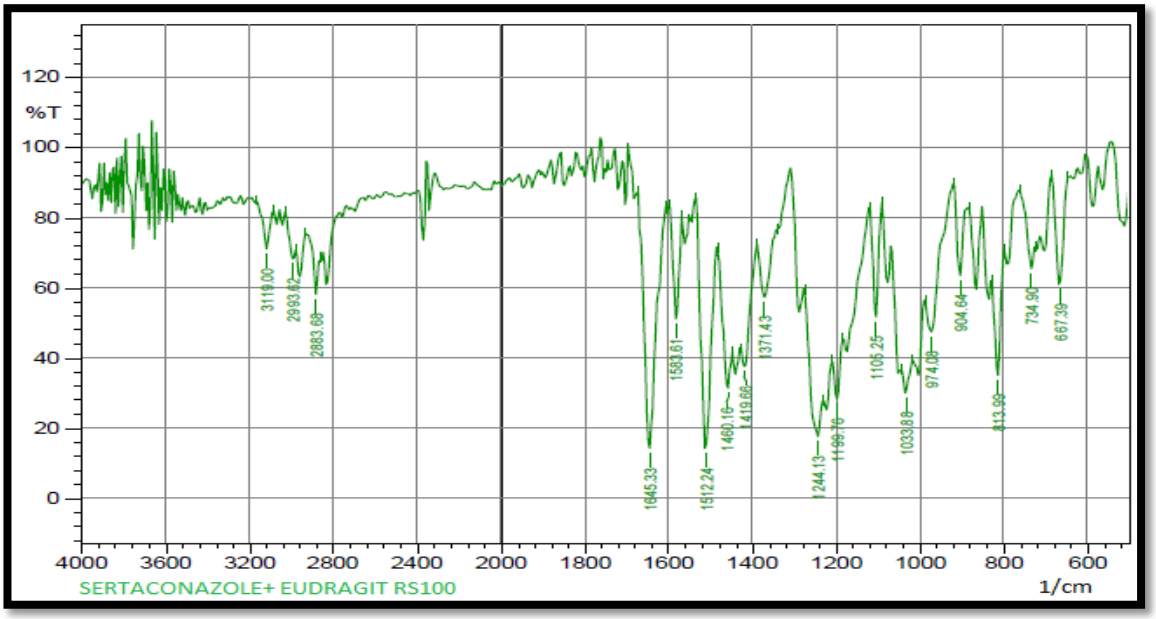


Figure : 7.5 FTIR spectra of drug+ polymer



Preparation of microsponges

Free flowing powder particles of Sertaconazole were obtained by quasi-emulsion solvent diffusion method with Eudragit RS 100 in ethyl alcohol. The quasi-emulsion solvent diffusion method used for the preparation of the microsponges was simple reproducible, and rapid. Surface morphology by SEM observed in fig 12. revealed the micro porous nature of microsponges.

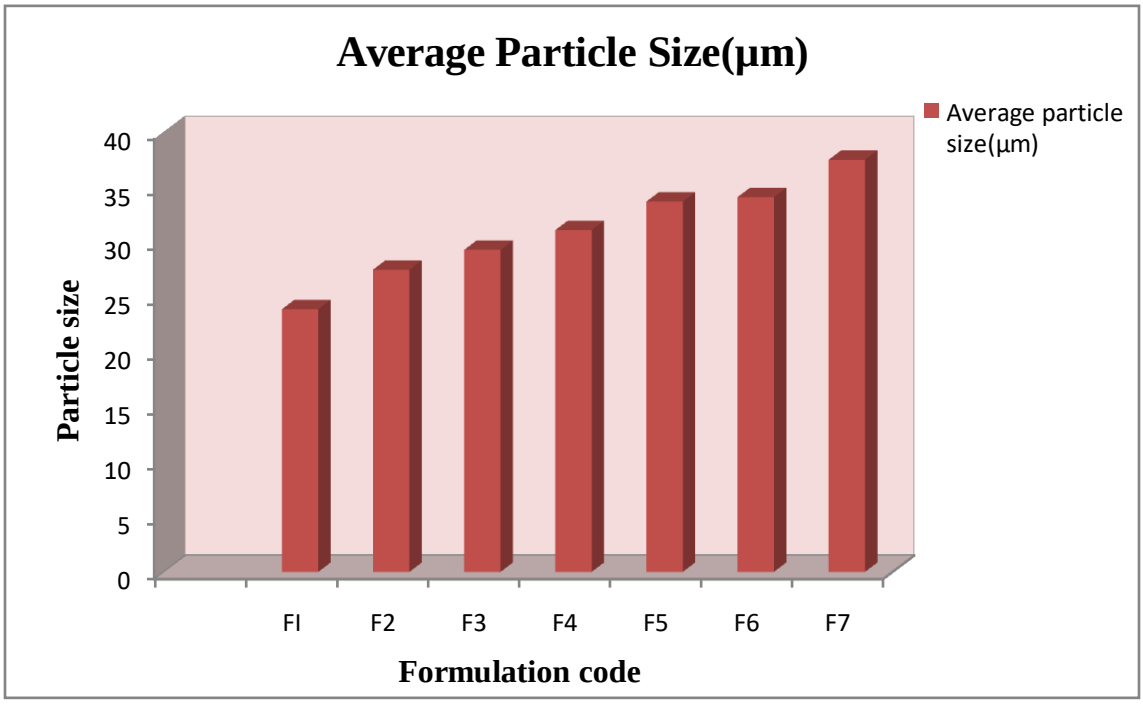
Figure: 7.6 Different formulations of microsponges

Evaluation of Sertaconazole microsponges

Table 10. Average particle size of Sertaconazole microsponges

Formulation code	Average particle size(µm) (Mean± SD)n=3
FI	23.9±1.02
F2	27.5±1.05
F3	29.3±1.54
F4	31.1±1.32
F5	33.7±1.25
F6	34.1±1.23
F7	37.5±1.19

Figure: 7.7 Average particle size distribution graph



RESULT

Visual inspection of all batches done using optical microscope for particle size analysis which shows that increased particle size with increase in drug : polymer ratio

Table: 11 Table revealing the results of Percentage Yield, Encapsulation Efficiency And % Drug Content

SL. NO:	Formulation code	Percentage yield ±SD	Encapsulation efficiency ±SD	% Drug content (conc*dil.factor*100)
1	F1	60 ± 0.23	79.94	39.97
2	F2	71.6± 0.13	86.93	57.95
3	F3	73.7± 0.18	91.89	68.93
4	F4	75.4± 0.016	94.28	74.42
5	F5	77.2± 0.12	95.39	79.19
6	F6	79 .9± 0.42	96.41	81.23
7	F7	81.5± 0.02	98.25	85.42

RESULT

The drug content in each formulation were analysed spectrometricaly and it was observed that all the formulation showed satisfactory drug content values ranging from 39.97% to 85.42 % as given in the table 11. Percentage yield of all batches of microsponges ranged from 60±0.23 to 81.5±0.02. Encapsulation efficiency of all 7 batches ranging from 79.9 to 98.2.

Figure: 7.8 Percentage yield graph

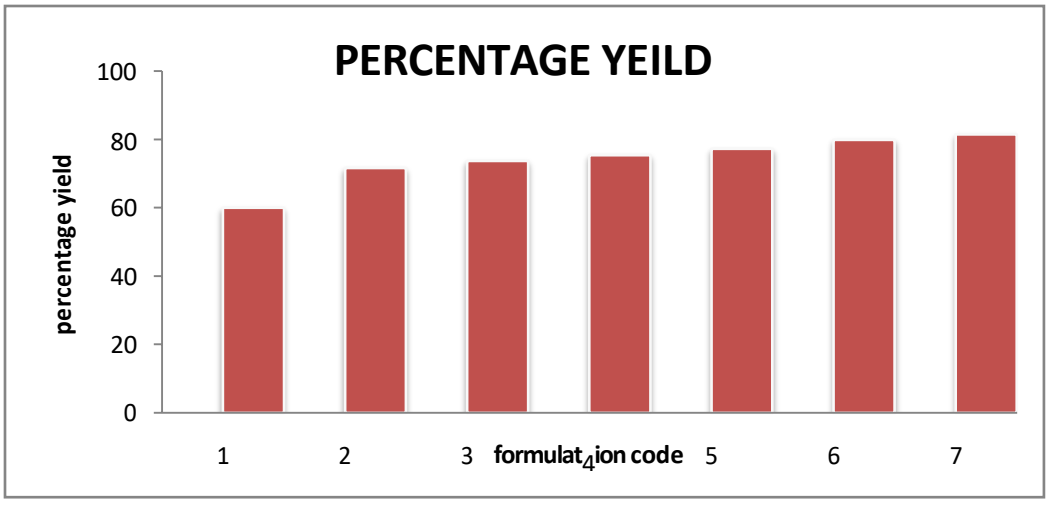


Figure: 7.9

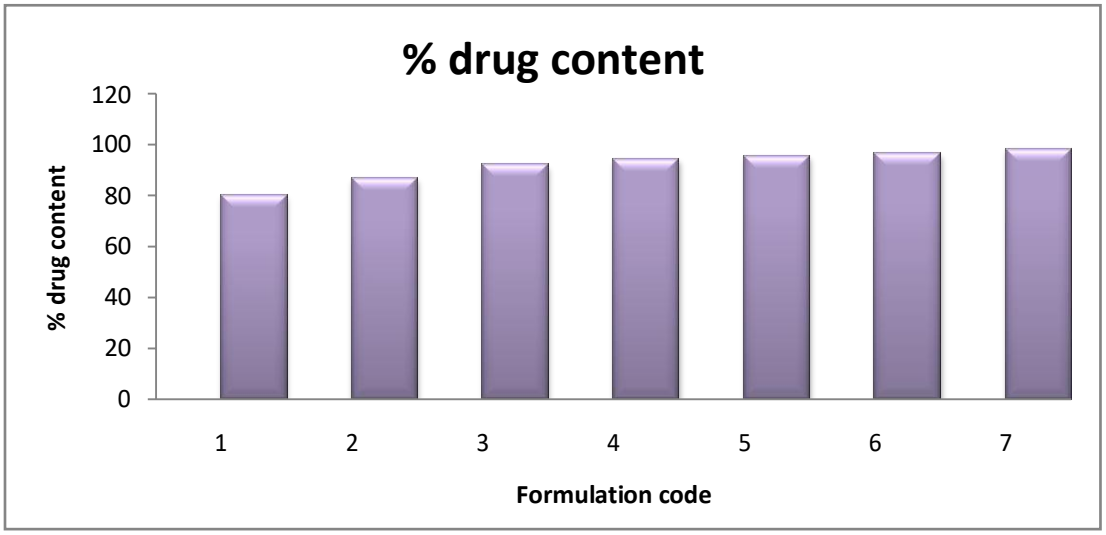


Figure: 7.10

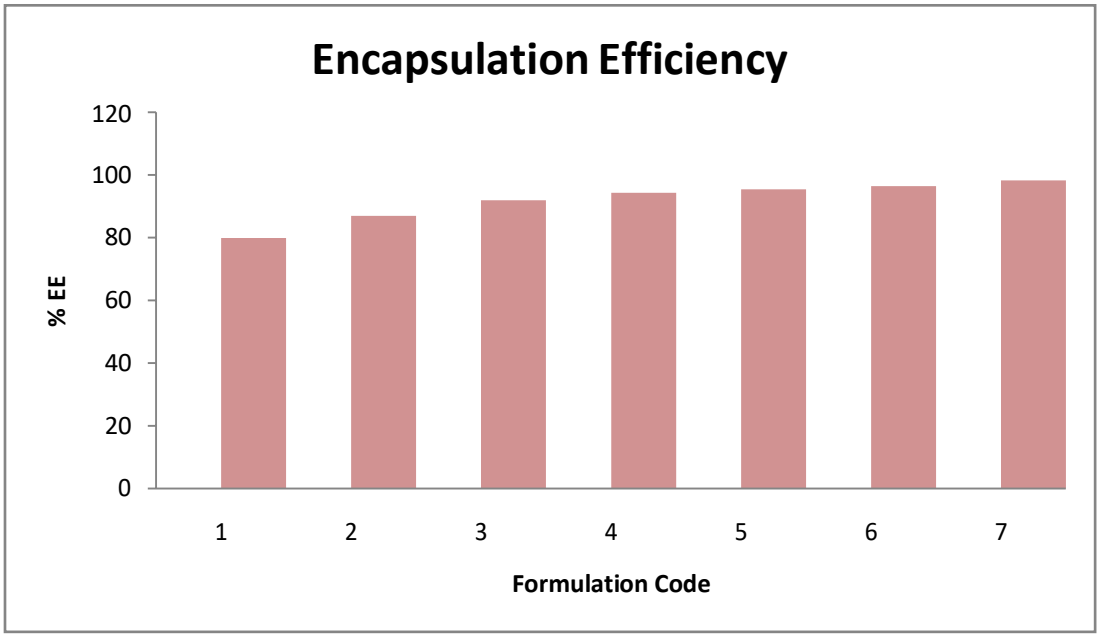


Figure: 7.11

SEM Photographs Of Sertaconazole Microsponges

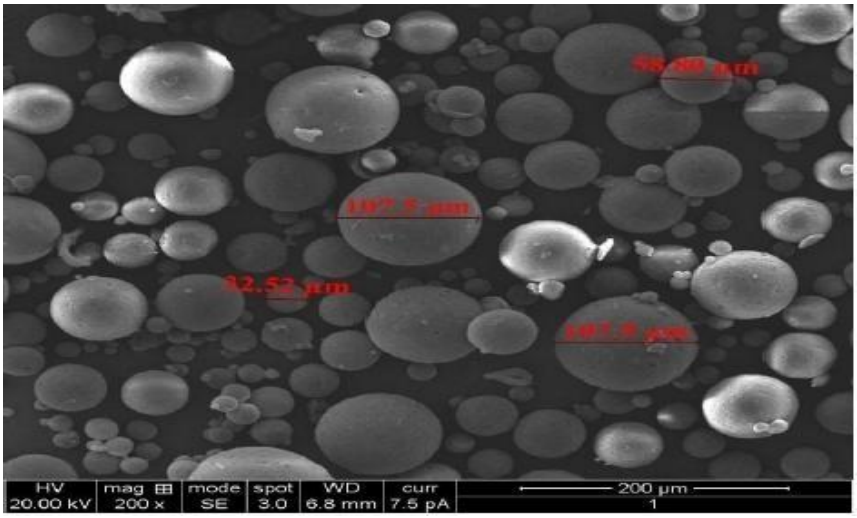


Figure: 7.12

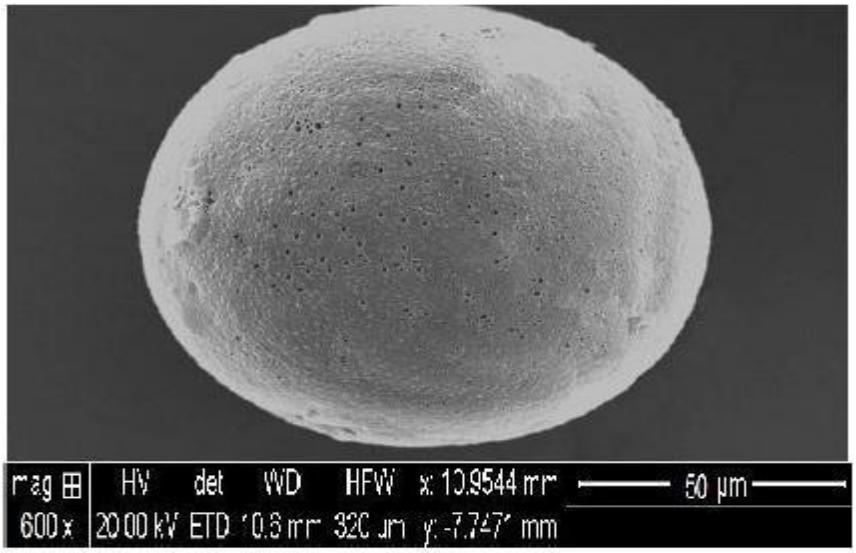
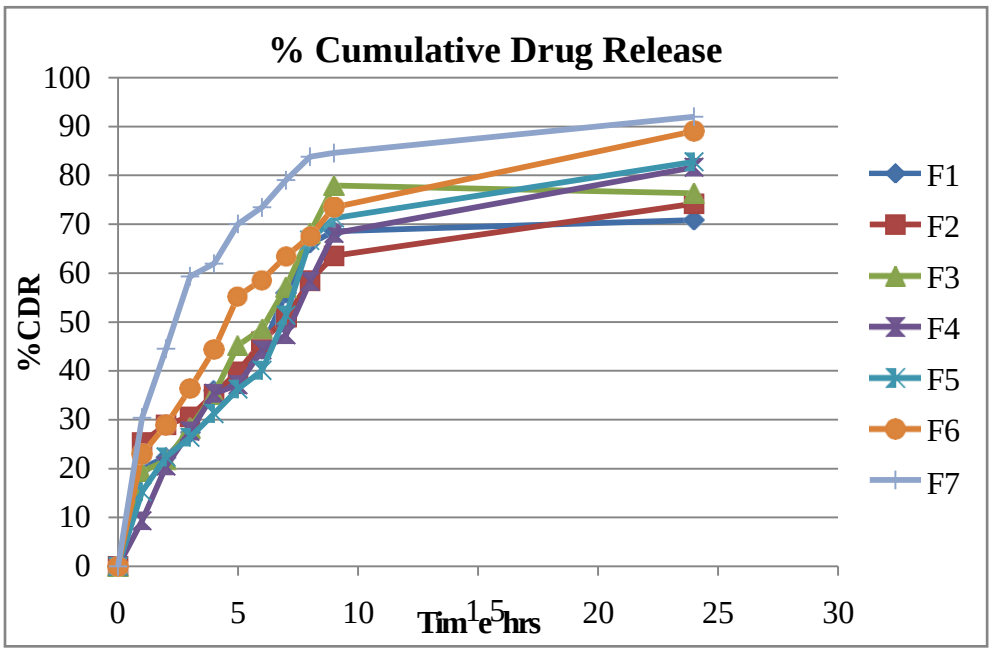


Table: 12

Cumulative % Drug Release of Sertaconazole Microsponge In Different Formulations

Time(hr)	% Cumulative Drug Release						
	F1	F2	F3	F4	F5	F6	F7
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	20.11	25.36	19.36	9.28	15.25	23.01	30.42
2	22.36	28.95	21.69	20.48	22.36	28.95	44.53
3	27.38	30.58	28.36	27.65	26.36	36.37	59.37
4	36.11	35.23	35.28	35.36	31.25	44.36	61.97
5	38.48	39.85	45.23	37.15	36.25	55.36	63.82
6	44.53	46.00	48.58	44.25	40.10	58.63	73.47
7	55.96	50.85	57.15	47.36	51.36	63.46	79.04
8	66.05	58.48	68.25	58.30	66.80	67.54	83.86
9	68.56	63.56	77.93	68.14	71.25	73.48	84.60
24	70.88	74.22	76.36	81.64	82.75	89.06	92.03

Figure: 7.13 Cumulative % Drug Release of Sertaconazole Microsponges In Different Formulations



RESULT

The cumulative % release from the formulation was in the range of 70.88% - 92.03%. From the seven formulation namely F_7 shows satisfactory sustained effect and a maximum drug release of about 92.03% in 24 hrs was seen. So this formulation is selected for further kinetic studies.

RELEASE KINETICS OF *SERTACONAZOLE MICROSPONGE* IN FORMULATION F_7

Consolidation Chart Of Kinetic Study Of F_7 Formulation

Table: 13 Consolidation Chart Of Kinetic Study Of F_7 Formulation

Time(hr)	ABS	CON	Amt. 900ml	Cum. Amt. of Drug	%CDR	Log %CDR	%CDR RT	Log % CDR T RT	Log Time	SQRT Time
0	0	0	0	0	0	0	0	0	0	0
1	0.0082	0.32031	0.2883	0.6086	30.4297	1.4833	69.5703	1.8424	0	1
2	0.012	0.46875	0.4219	0.8906	44.5313	1.6487	55.4688	1.7440	0.3010	1.4142
3	0.016	0.625	0.5625	1.1875	59.3750	1.7736	40.6250	1.6088	0.4771	1.7320
4	0.0167	0.65234	0.5871	1.2395	61.9727	1.7922	38.0273	1.5801	0.6020	2
5	0.0172	0.67188	0.6047	1.2766	63.8281	1.8050	36.1719	1.5584	0.6989	2.2360
6	0.0198	0.77344	0.6961	1.4695	73.4766	1.8661	26.5234	1.4236	0.7781	2.4494
7	0.0213	0.83203	0.7488	1.5809	79.0430	1.8979	20.9570	1.3213	0.8450	2.6457
8	0.0226	0.88281	0.7945	1.6773	83.8672	1.9236	16.1328	1.2077	0.9030	2.8284
9	0.0228	0.89063	0.8016	1.6922	84.6094	1.9274	15.3906	1.1873	0.9542	3
27	0.0248	0.96875	0.8719	1.8406	92.0313	1.9639	7.9688	0.9014	1.3802	4.8989

Figure: 7.14 Zero order plot of f_7 formulation

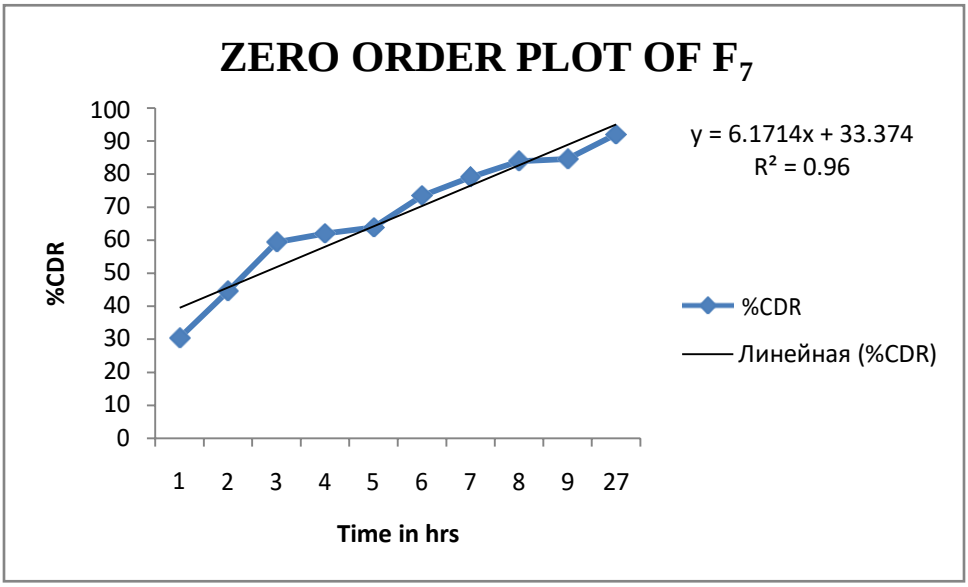


Figure: 7.15 First order plot of F_7 formulation

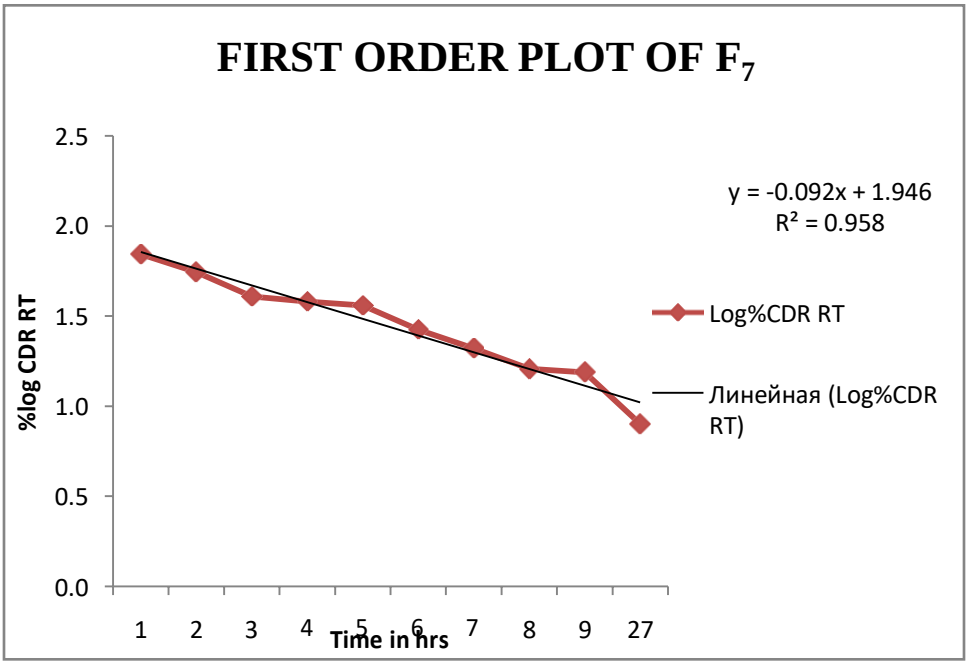


Figure: 7.16 Higuchi plot of F_7 Formulation

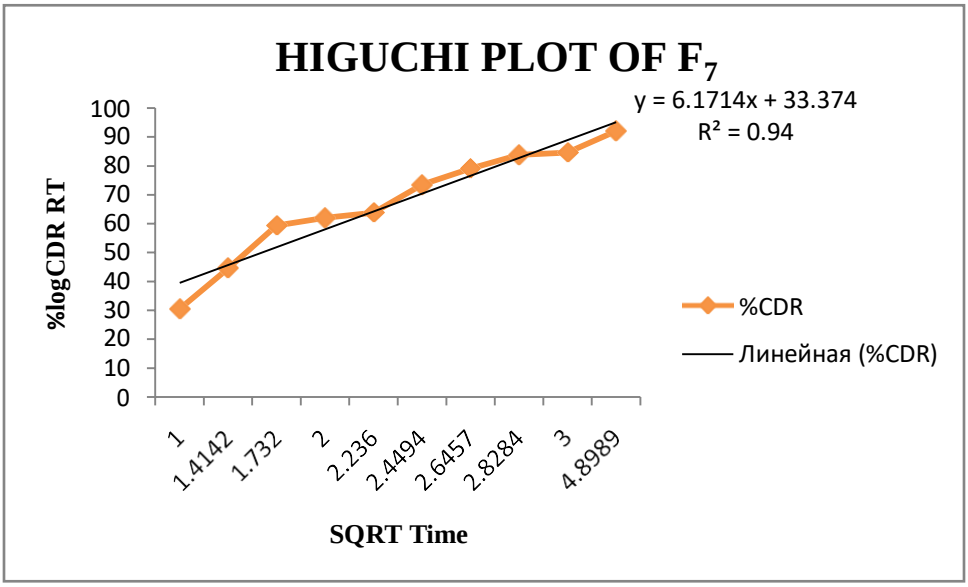
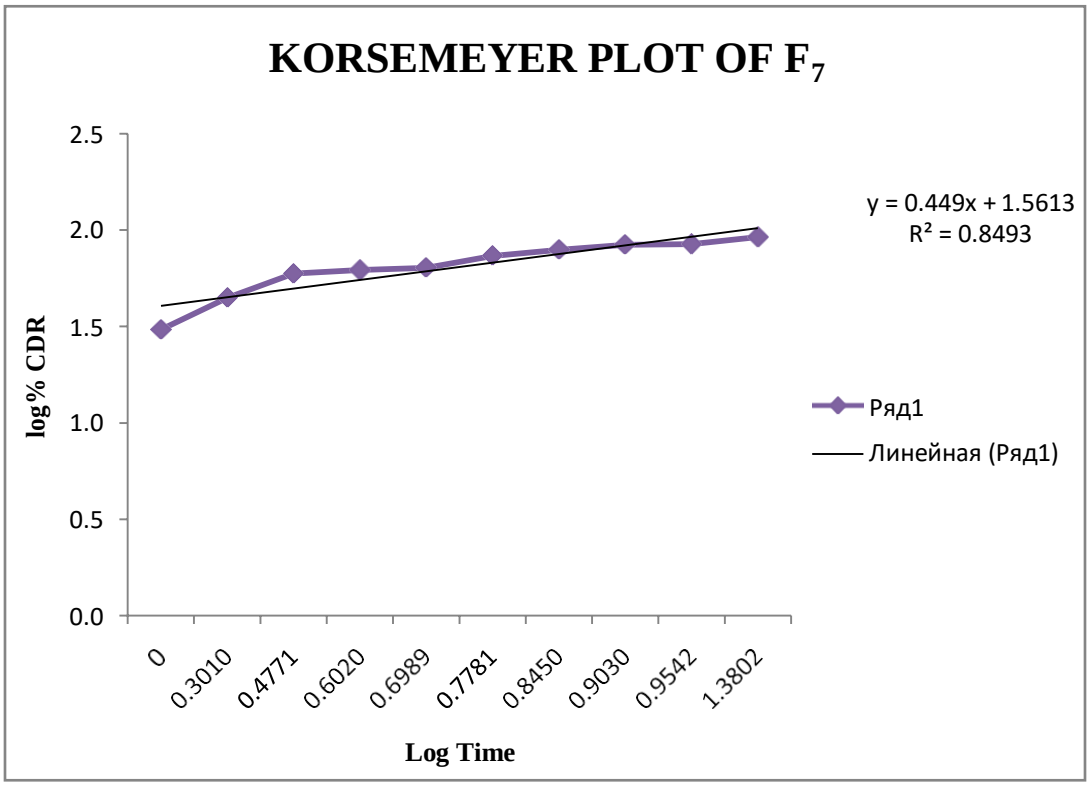


Figure: 7.17 Korsemeyer plot of F_7 formulation



REGRESSION COEFFICIENT (R^2) VALUES OF KINETIC MODEL FOR FORMULATION F_7

Table: 14 Regression Coefficient (r^2) values of Kinetic model for formulation f7

Formulation	KINETIC DRUG RELEASE		MECHANISM OF RELEASE		
	ZERO ORDER	FIRST ORDER	HIGUCHI	KORSEMEYER PEPPAS	
	Correlation Coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Slope 'n' value	Correlation coefficient (r^2)
F7	0.96	0.95	0.94	0.44	0.84

RESULT

The in vitro drug release showed highest regression value for the zero order kinetics and release data was best fit with Higuchi model kinetics because the value of r^2 was greater in this model. The formulation follows the diffusion controlled mechanism for drug release. The n value was found to be 0.44, indicating that the drug release mechanism was diffusion and non fickian release.

Table: 15

EVALUATION OF SERTACONAZOLE MICROSPONGE GEL.

Visual inspection	Clear, transparent gel, viscous in nature with smooth texture, good homogeneity
Spreadability	14.2±0.81
pH	6.5
Viscosity	265.5 cPs

Table: 16

% Drug Content of Sertaconazole Gel Formulation

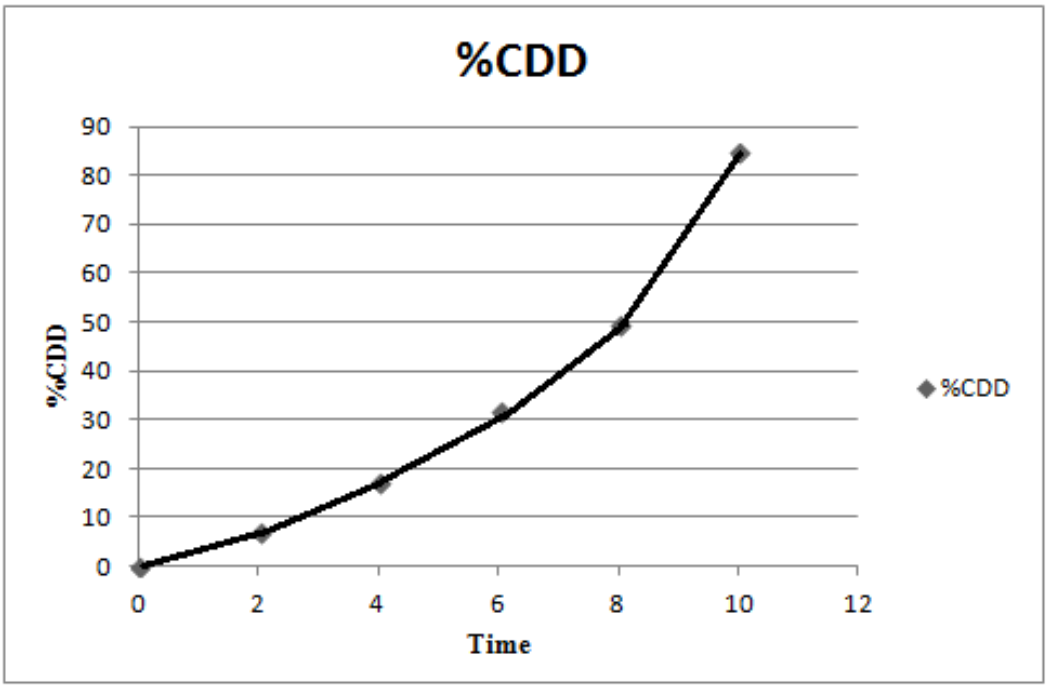
Sl. No	abs	Conc(abs/slope) mg/ml	%Drug content(conc*dil.factor*100)
1	0.422	785.1 ± 0.23	78.1±0.01
	0.423		
	0.422		

Table: 17

Permeability Study Data Of Sertaconazole Gel.

Time (hr)	Abs	Conc	ADD	%ADD	%Cum.Drug. Diffused
0	0	0	0	0	0
2	0.036	1.4062	14.0625	7.0312	7.0312
4	0.052	2.0312	20.3125	10.1562	17.1875
6	0.074	2.8906	28.9063	14.4531	31.6406
8	0.091	3.5546	35.5469	17.7734	49.4140
10	0.18	7.0312	70.3125	35.1562	84.5703

Figure: 7.18 % Cumulative Drug Diffused



8. DISCUSSION

8.1 PREFORMULATION PARAMETERS

8.1.1 Anaytical Method

The standard c calibration curve is generated using Microsoft Excel 2007 by plotting concentration verses absorbance. The experiment was performed in triplicate and average values with standard deviation were reported. The method obeys Beer-Lambert's law in range of 5-30µg/ ml. This data was further used for the calculation.

8.1.2 Melting Point

The melting point of Sertaconazole was pragmatic in range of 145-150^{0}C (Literature standard 147°C). As experimental values were in good agreement with standard, procured drug was supposed to be pure.

8.1.3 Organoleptic Properties

By determining the organoleptic properties, it was observed that the drug was found to be white colour, and odourless. Solubility study showed that Sertaconazole is practically insoluble in water, soluble in methanol, sparingly soluble in alcohol and methelene chloride.

8.1.4 Compatibility Studies

FT-IR study revealed that drug loading occurred in the microsponges as both polymer and drug peaks have been observed. No significant deviation in the peaks was observed which indicated that there is no incompatibility between drug and formulation component.

8.2 Microsponges

In quasi emulsion solvent diffusion method affinity between good solvent and drug is stronger than the affinity between good solvent and poor solvent. Drug solution in the good solvent formed emulsion droplets (quasi) upon pouring into the poor solvent and the organic phase then diffused out in to the external phase resulting in the formation of

pores in the micron-sized particles, known as microsponges that have taken a spherical shape due to constant stirring.

Free flowing spherical microsponges were obtained by quasi emulsion solvent diffusion method with Eudragit RS100. The method seems to be promisingfor the preparation of Sertaconazole microsponges.

8.2.1 Physical appearance

Microsponge particle with fairy white tincture were obtained by Quasi emulsion solvent diffusion method. With good flow properties than as compared with pure drug.

8.2.2 Production Yield, Encapsulation Efficiency and % Drug Content

The production yield of all batches of microsponges ranged from 37.5±0.23 to 56.87±0.02. It reflected that higher the drug :polymer ratio higher the production yield. This was due to a bridged ethyl alcohol diffusion rate from concentrated solutions to aqueous phase at higher drug: polymer concentration which provide additional time for formation of droplet, thereby improving yield.

The mean amount of drug entrapped in fabricated microsponges was found to be lesser than theoretical value for every drug: polymer ratio employed, in view of the fact that drug encapsulation efficiency did not attain 100%. This was for the reason that some drug gets dissolved in aqueous phase or solvent used. Encapsulation efficiency outcome reflects that higher the drug polymer ratios leads to superior drug loadings. Here the encapsulation efficiency ranging from 62.2 to 76.1.

8.2.3 Scanning Electron Microscopy (SEM)

For morphology and surface topography investigation prepared micro sponge were subjected to SEM analysis. The captured SEM image of microsponges is shown in figure; 17, 18. SEM results indicated that microsponges formed were highly pours, predominantly spherical and not much entire sertaconazole crystals were observed visually. Pores were induced by diffusion of solvent from surface of microsponges.

8.2.4 Particle Size Analysis

Visual inspection results of all batches done using optical microscope for particle size discovered increased particle size with increase in drug: polymer ratio. It might be since polymer available at higher drug: polymer ratio was in more amount thereby increasing polymer wall thickness which leads to larger size of microsponges.

8.2.5 Analysis of Release Mechanism

The drug release mechanism was analysed by fitting the release data in to various equation like first order, zero order, Higuchi, Korsmeyer – Peppas, and by highest r^2 value best fit model was decided. Depending upon the % cummulative drug release chart found that formulation F7 has the maximum release (92.03).this formulation was taken as further study.

The in vitro drug release showed highest regression value for the zero order kinetics and release data was best fit with Higuchi model kinetics because the value of r^2 was greater in this model. The formulation follows the diffusion controlled mechanism for drug release.

The in vitro drug release data were fitted to korsemyer peppas model. The n value was found to be 0.44, indicating that the drug release mechanism was diffusion and non fickian release.

8.3 Evaluation of Sertaconazole Microsponge Gel

8.3.1 Visual Inspection

The prepared gel formulations of sertaconazole microsponges were inspected visually for their colour, texture and appearance. The prepared formulation were clear, transparent gel, viscous in nature with smooth texture and of good homogeneity with no any lumps.

8.3.2 pH Measurement

The pH value of prepared formulation was found in the range of 6.5, which are supposed to be suitable to pass up threat of nuisance on application to skin.

8.3.3 Spreadability Study

The spreadability of the formulated sertaconazole gel is 14.2 .The findings of spreadability depicted that formulated gel get easily spread on applying small amount of shear. Which indicating that spreadability of drug loaded microsponge gel was good.

8.3.4 Viscosity Measurements

The viscosity of prepared microsponge gel was found to be 265.5 cPs. Which was measured by Brookfield viscometer, then the viscosity was found to be reliant on polymeric content of formulation.

8.3.6 Diffusion Pattern of Sertaconazole from Gel Formulation Incorporated With Sertaconazole Microsponges

Incorporation of sertaconazole in the form of microsponges in to the gel formulation had a significant effect on the rate of release from the microsponges. The microsponges with drug: polymer ratio 1:7 was selected for the further incorporation in to gel formulation. Incorporation of the sertaconazole microsponges into the gel formulation resulted in decrease rate of drug release from the microsponges when compared to the release from the sertaconazole microsponges alone, This may be due to the increased path for the drug to pass through the cellophane membrane. which means the drug first has to be release from the microsponges to the gel base and then from the there on to the skin hence the time of release was high.

CONCLUSION

- In this work an attempt was made to formulate and evaluate microsponges for controlled release of Sertaconazole by Quasi emulsion solvent diffusion method.
- The ratio of drug: polymer required to produce microsponges with good encapsulation efficiency was found to be from F7. Below this ratio, the microsponges formed had low capacity encapsulation of the drug and above this range there was no further increase in the encapsulation efficiency. Hence it was concluded that F7 was optimum ratio of drug: polymer to produce good microsponges.
- By the drug release studies of the formulation F7 was concluded that the release profile was sustained and was in controlled fashion.
- The prepared sertaconazole microsponge formulations were evaluated for drug content, in vitro drug release studies and invitro release kinetics. The best formulation was found to be F7. The pharmacokinetic model reveals that the mechanism of drug release from microsponges formulation was Higuchi model.
- The selected formulation were incorporated into carbopol 940 gel base and evaluated for viscosity, spredability and diffusion studies.
- Finally we may concluded that formulation F7 was best formulation to obtain good microsponges and sustain release of drug.

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